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(54) **MODULATION OF PRE-MRNA USING SPLICE MODULATING OLIGONUCLEOTIDES AS THERAPEUTIC AGENTS IN THE TREATMENT OF DISEASE**

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C07H 21/02 (2006.01)

(52) **U.S. Cl.**
USPC **536/23.1**; 536/24.5; 536/241

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention encompasses a class of compounds known as splice modulating oligonucleotides (SMOs) that modulate pre-mRNA splicing, thereby affecting expression and functionality of a specific protein in a cell. The present invention further provides compositions and methods for modulating pre-mRNA splicing using a SMO of the invention to abrogate disease-causing mutations in a protein. Accordingly, the present invention provides compositions and methods of treating a subject at risk of, susceptible to, or having a disease, disorder, or condition associated with aberrant or unwanted target pre-mRNA expression or activity.

20 Claims, 8 Drawing Sheets

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Figure 1

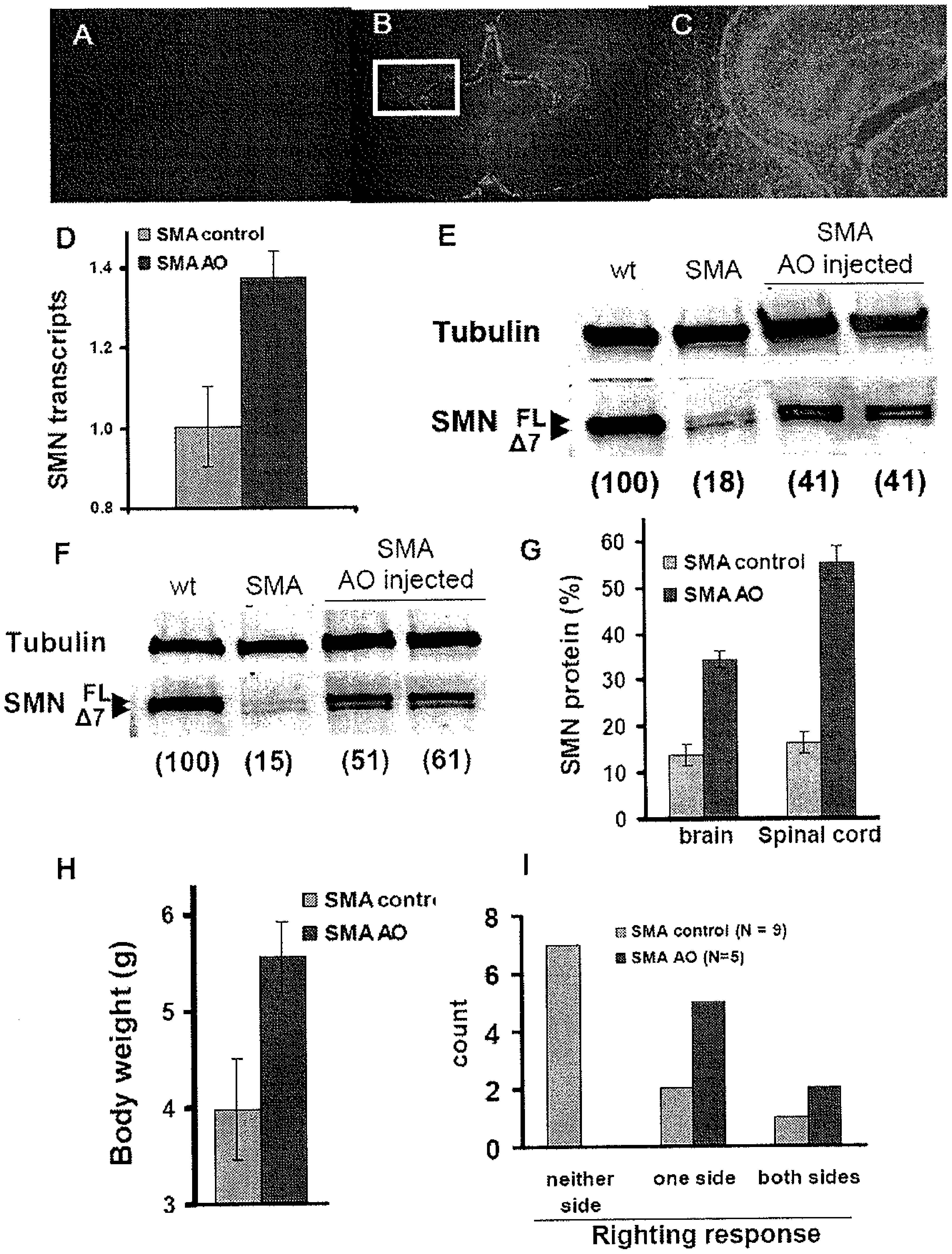

A
B
C
D
SMA control
SMA AO
SMN transcripts
1.4
1.2
1.0
0.8
E
wt
SMA
SMA AO injected
Tubulin
SMN FL Δ7
(100) (18) (41) (41)
F
wt
SMA
SMA AO injected
Tubulin
SMN FL Δ7
(100) (15) (51) (61)
G
SMA control
SMA AO
SMN protein (%)
60
50
40
30
20
10
0
brain
Spinal cord
H
SMA contr
SMA AO
Body weight (g)
6
5
4
3
I
SMA control (N = 9)
SMA AO (N=5)
count
8
6
4
2
0
neither side
one side
both sides
Righting response

Figure 2

Alternative splicing at the flip-flop cassette exons of GluR subunits of AMPA receptors

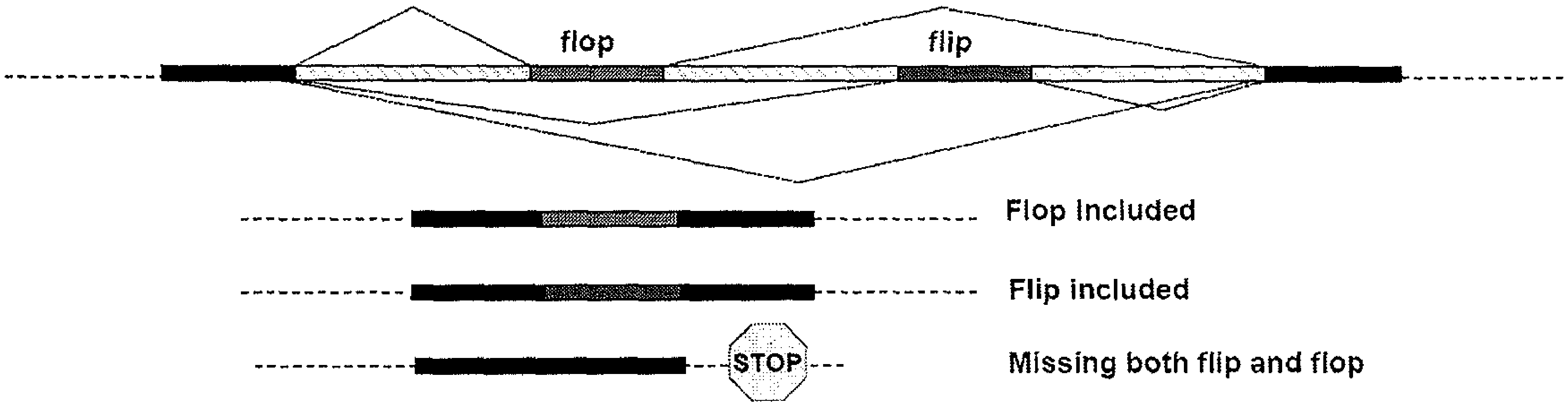
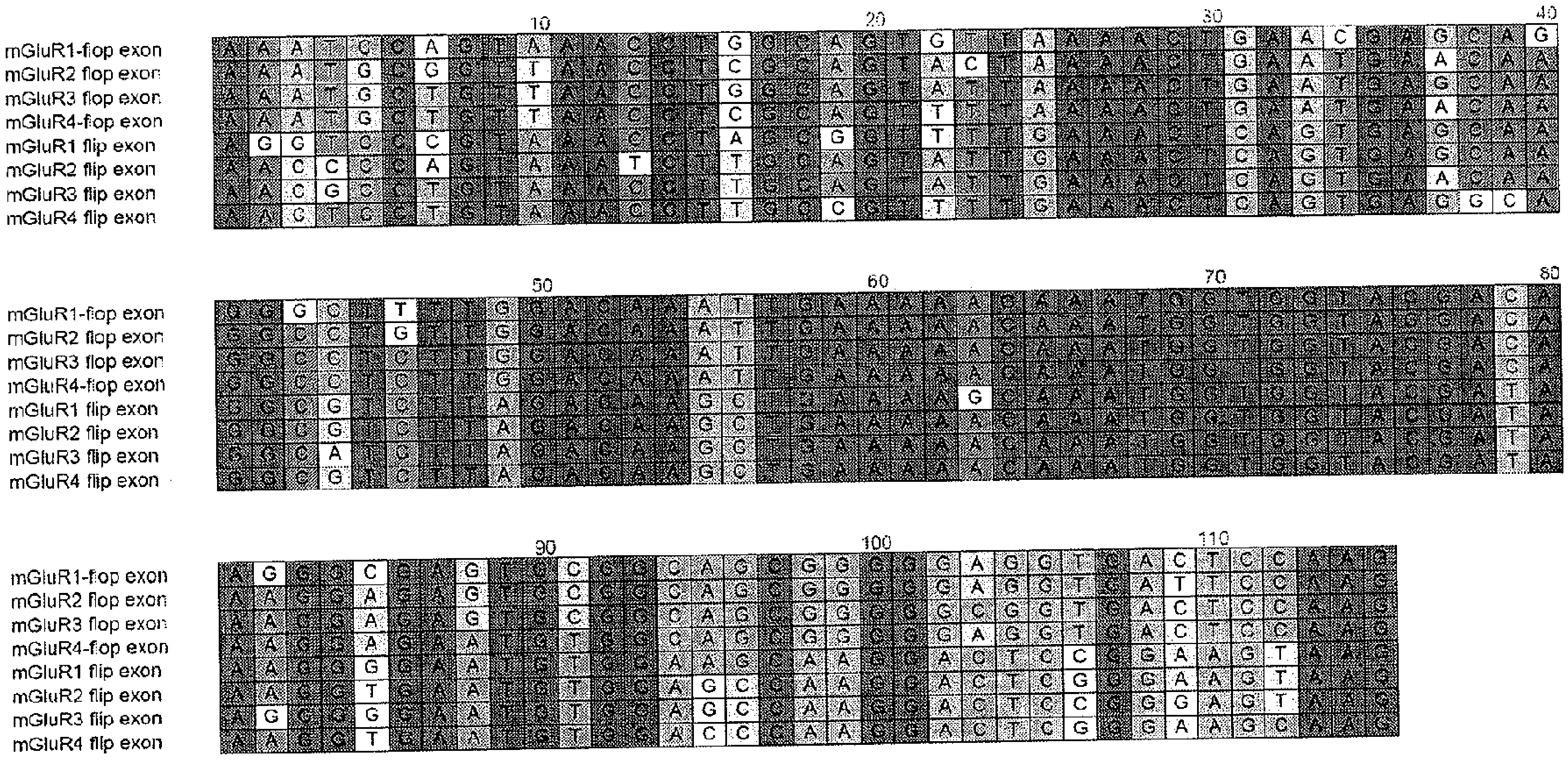


Figure 3


10
20
30
40
50
60
70
80
90
100
110
mGluR1-flop exon
mGluR2 flop exon
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mGluR4-flop exon
mGluR1 flip exon
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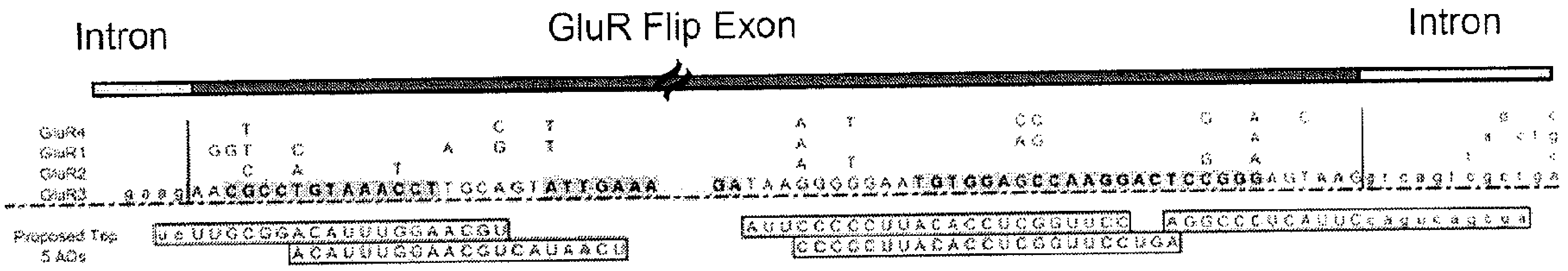
mGluR3 flip exon
mGluR4 flip exon

Figure 4


Intron
GluR Flip Exon
Intron
GluR4
GluR1
GluR2
GluR3
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GATAAGGGGGAATGTGGAGCCAAGGACTCCGGGAGTAAGgtcagtcgctga
Proposed Top 5 AOs
ucUUGCGGACAUUUGGAACGU
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AUUCCCCCUUACACCUCGGUUCC
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AGGCCCUCAUUCcagucagcga

Figure 5

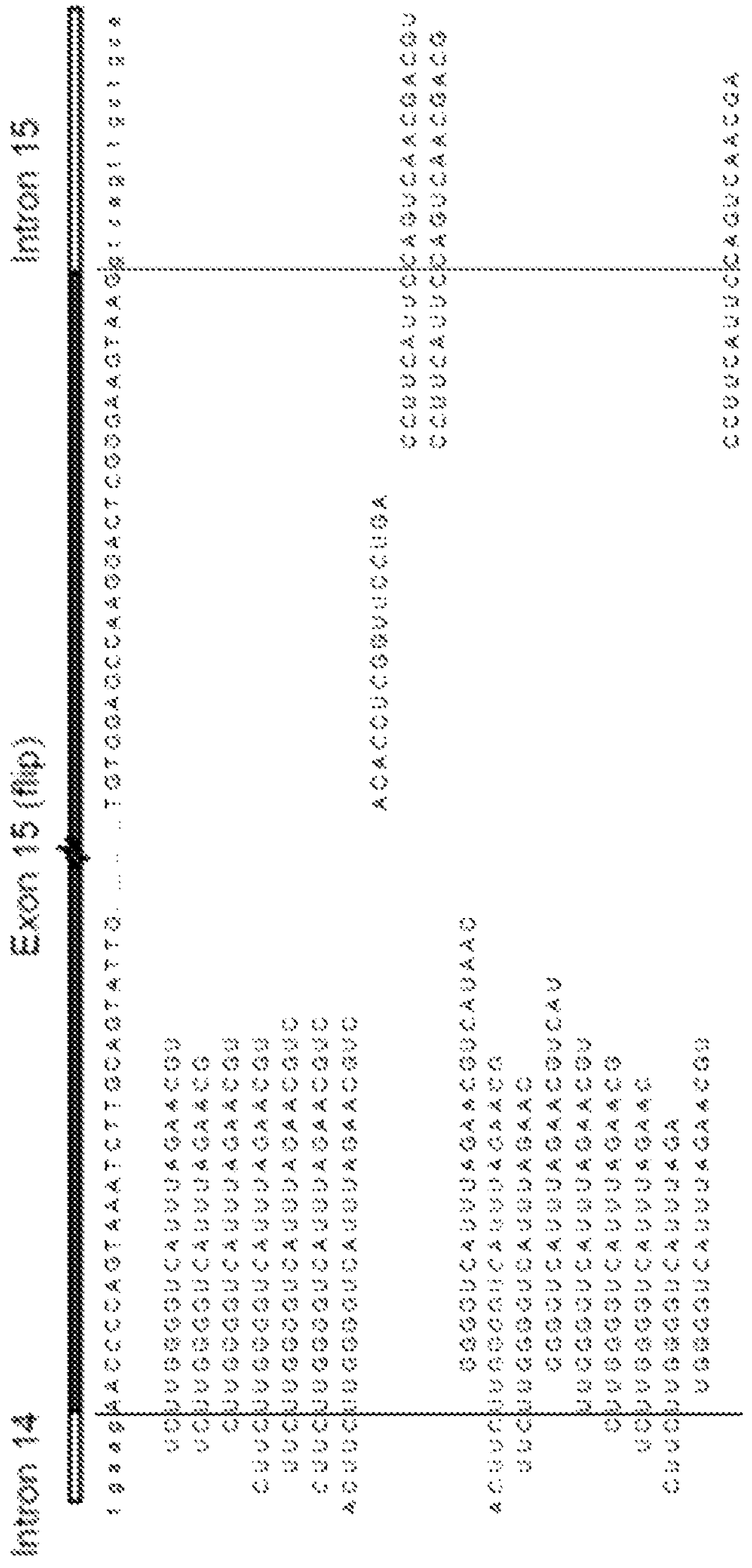
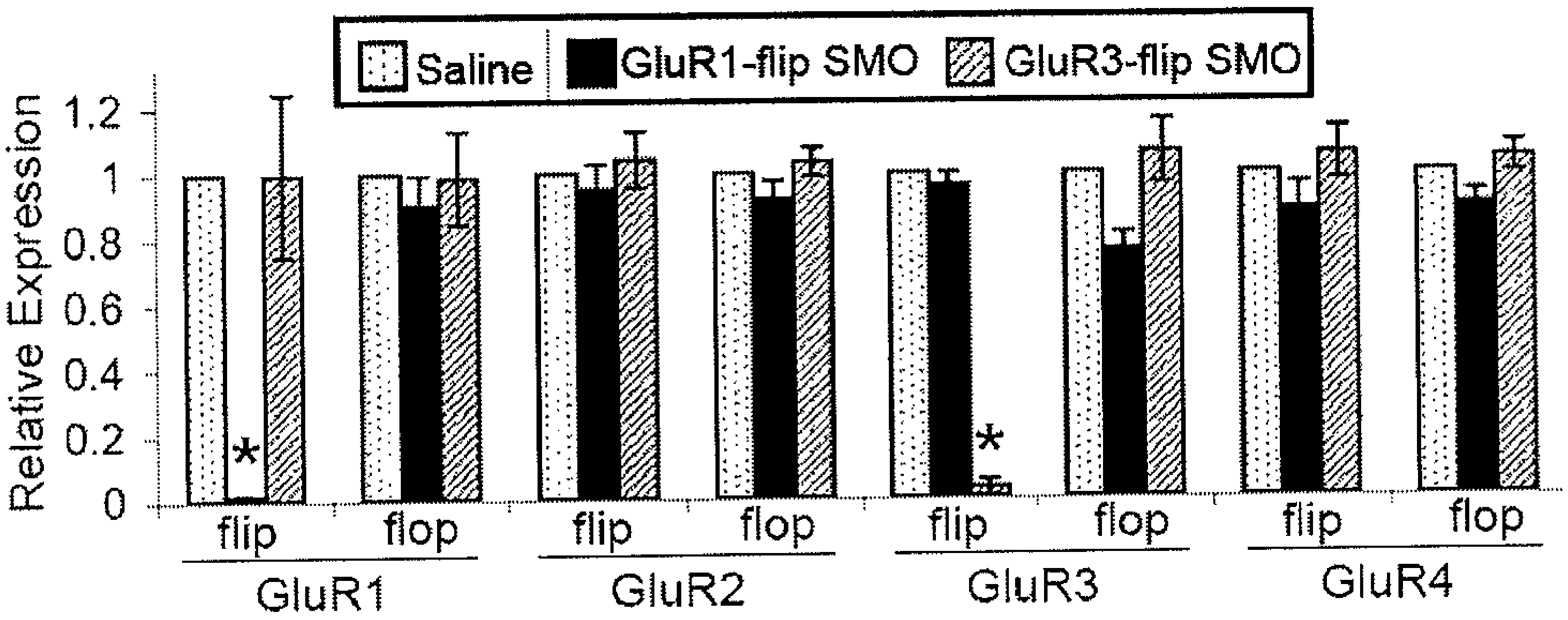


Figure 6



Saline
GluR1-flip SMO
GluR3-flip SMO
Relative Expression
1.2
1
0.8
0.6
0.4
0.2
0
*
*
flip
flop
flip
flop
flip
flop
flip
flop
GluR1
GluR2
GluR3
GluR4

Figure 7

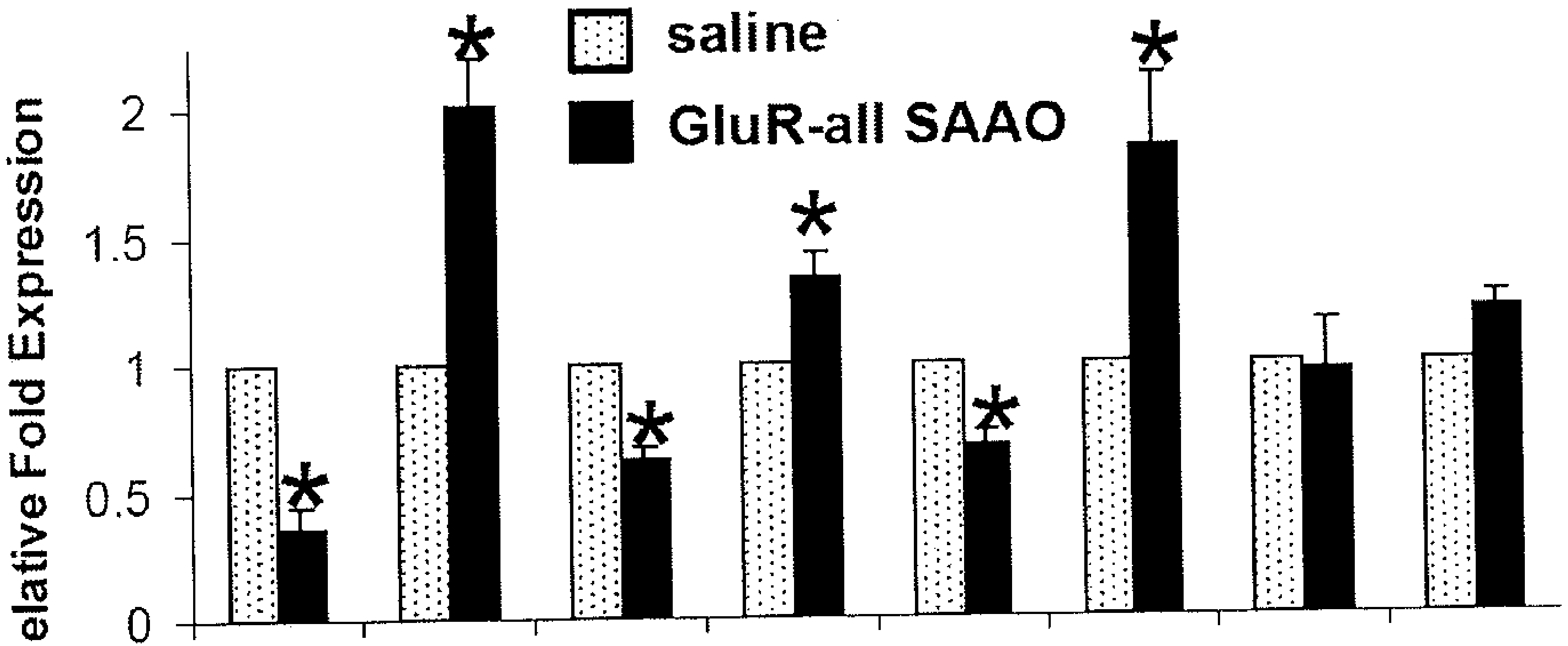
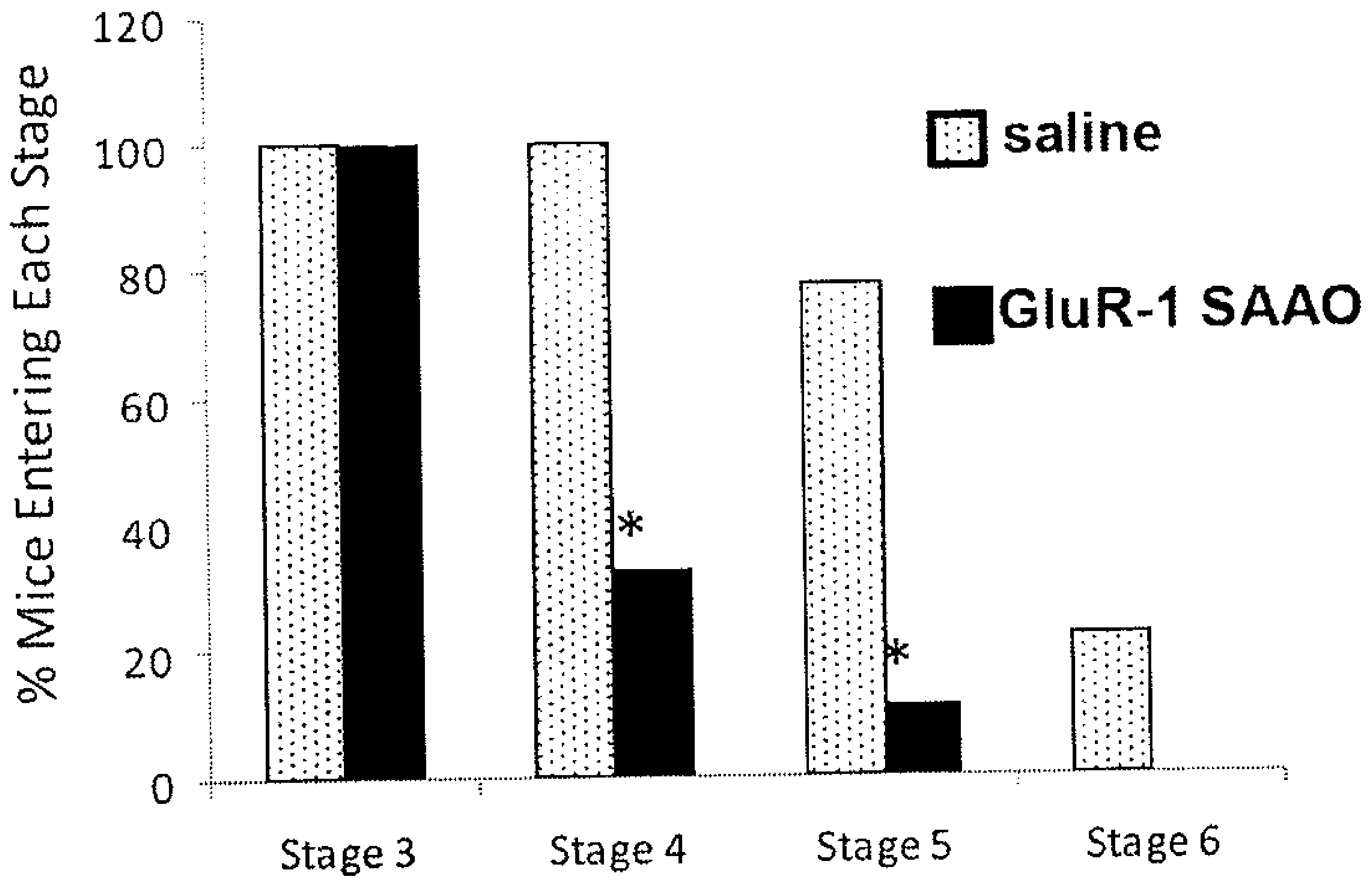

saline
GluR-all SAAO
Relative Fold Expression
0
0.5
1
1.5
2
*
*
*
*
*
*
flip
flop
flip
flop
flip
flop
flip
flop
GluR1
GluR2
GluR3
GluR4

Figure 8


% Mice Entering Each Stage
120
100
80
60
40
20
0
Stage 3
Stage 4
Stage 5
Stage 6
*
*
saline
GluR-1 SAAO

MODULATION OF PRE-MRNA USING SPLICE MODULATING OLIGONUCLEOTIDES AS THERAPEUTIC AGENTS IN THE TREATMENT OF DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage of International Patent Application No. PCT/US2010/021078, filed Jan. 14, 2010, which claims the benefit of the priority of U.S. Provisional Patent Application No. 61/144,543, filed Jan. 14, 2009, which applications are incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under Grant No. NIH 1R21NS064223-01A1 awarded by the National Institutes of Health. The U.S. Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Approximately 90,000 known human proteins are the product of about 20,000 human genes. It is estimated that roughly 75% of human genes are subject to alternative splicing. Alternative splicing is the process responsible for this remarkable diversity of protein expression in general as well as tissue-specific expression of proteins. DNA is initially transcribed "literally" into pre-messenger RNA (pre-mRNA) comprising introns and exons. The average human protein coding gene is 28,000 nucleotides long with 8.8 exons separated by 7.8 introns. Exons are about 120 nucleotides long while introns are anywhere from 100-100,000 nucleotides long. Pre-mRNA is first processed by a spliceosome which recognizes where introns begin and end, removes introns, and joins exons together to form a mature mRNA that is then translated into a protein.

Pre-messenger RNA splicing is an essential process required for the expression of most genes. Improperly spliced mRNA molecules lead to altered proteins that cannot function properly, resulting in disease. Alternative splicing errors are known to contribute to cancer and many neurological diseases, including β-thalassemia, cystic fibrosis, spinal muscular atrophy (SMA), growth deficiencies, ataxia, autism, and muscular dystrophies.

5HT2CR: Prader-Willi syndrome (PWS)

Prader-Willi syndrome (PWS) is a genetic disorder caused by the deletion of paternal copies of several genes on the 15th chromosome located in the region 15q11-13 leading to deletion of a small nucleolar ribonucleoprotein (snoRNA), HBII-52. Deletion of the same region on the maternal chromosome causes Angelman syndrome. The incidence of PWS is about 1 in 12,000 to 1 in 15,000 live births. Phenotypically, individuals afflicted with PWS typically exhibit significant cognitive impairment, hyperphagia often leading to morbid obesity, an array of compulsive behaviors, and sleep disorders.

After transcription, nascent or pre-mRNA undergoes a series of processing steps in order to generate a mature mRNA molecule. snoRNAs are non-protein coding RNAs that are 60-300 nucleotides (nt) long and that function in guiding methylation and pseudouridylation of ribosomal RNA (rRNA), small nuclear RNAs (snRNAs), and transfer RNAs (tRNAs). Each snoRNA molecule acts as a guide for only one (or two) individual modifications in a target RNA. In order to carry out the modification, each snoRNA associates with at least four protein molecules in an RNA/protein complex referred to as a small nucleolar ribonucleoprotein (snoRNP). The proteins associated with each RNA depend on the type of snoRNA molecule incorporated. The snoRNA molecule contains an antisense element (a stretch of 10-20 nucleotides) which are complementary to the sequence surrounding the nucleotide targeted for modification in the pre-RNA molecule. This enables the snoRNP to recognise and bind to the target RNA. Once the snoRNP has bound to the target site the associated proteins are in the correct physical location to catalyse the chemical modification of the target base.

The two different types of RNA modification (methylation and pseudouridylation) are directed by two different families of snoRNAs. These families of snoRNAs are referred to as antisense C/D box and H/ACA box snoRNAs based on the presence of conserved sequence motifs in the snoRNA. There are exceptions, but as a general rule C/D box members guide methylation and H/ACA members guide pseudouridylation. HBII-52, also known as SNORD115, belongs to the C/D box class of snoRNAs.

In the human genome, HBII-52 is encoded in a tandemly repeated array with another C/D box snoRNA, HBII-85, in the Prader-Willi syndrome (PWS) region of human chromosome 15q11-13. This locus is maternally imprinted, meaning that only the paternal copy of the locus is transcribed.

The snoRNA HBII-52 is exclusively expressed in the brain and is absent in PWS patients. HBII-52 lacks any significant complementarity with ribosomal RNAs, but does have an 18 nucleotide region of conserved complementarity to exon 5 of serotonin 2C receptor (5-HT2CR) pre-mRNA. snoRNA HBII-52 is an example of an RNA that regulates pre-mRNA splicing by binding to a splice supressor sequence of the 5-HT2CRgene, resulting in enhancement of exon 5b inclusion and the expression of a full-length, functional 5-HT2C receptor.

A recent study showed that these sequences co-varied among species, such that differences in nucleotides in one were always matched by complementary changes in the other; so that 100% complementarity is always present (Kishore and Stamm, 2006, Science 311:230-232). Kishore and Stamm, 2006, Science 311:230-232 also used a minigene construct to demonstrate that interaction of 5-HT2CRand HBII-52 at the consensus sequences is critical for appropriate splicing of the 5b exon so that a functional receptor is generated. When HBII-52 is mutated at sites that prevent its interaction with 5-HT2C, exon 5a is included and exon 5b is excluded. The splice variant containing 5a leads to a nonfunctional, out of frame, truncated transcript (Kishore and Stamm, 2006, Science 311:230-232).

Dysregulation of serotonergic systems appears to play a role in many cognitive disorders, including depression, autism, and obsessive compulsive disorder. Although a direct link between dysfunction of 5-HT2CRand PWS has yet to be demonstrated, 5-HT2CR knockout mice display phenotypic characteristics that are remarkably similar to those observed in PWS, including development of hyperphagia-induced obesity. In patients with PWS, satiety centers seem to be perturbed, leading to excessive overeating and obesity. Similarly, in 5-HT2C receptor knockout mice, obesity develops due to a lack of control of feeding behavior (Nonogaki et al., 1998, Nature Med. 4:1152-1156). 5-HT2CRagonists appear to be effective in inducing satiety (Nilsson, 2006, J. Med. Chem. 49:4023-4034). Another notable characteristic of patients with PWS is compulsive behavior. 5-HT2CR knockout mice also demonstrate compulsive-like behavior (Chou-Green et al., 2003, Physiol. Behav. 78:641-649). Interestingly, 5-HT2CR agonists are effective in animal models of obsessive-compulsive disorder (OCD); suggesting dysfunction of this receptor system could play a role in this disorder (Jenck et al., 1998, Expert. Opin. Invest. Drugs 7:1587-1599; Dunlop et al., 2006, CNS Drug Rev. 12:167-177). The sleep impairment observed in many PWS patients is also found in the 5-HT2CR knockout mouse (Frank et al., 2002, Neuropsychopharmacology 27:869-873). These mice also exhibited reduced hippocampal-dependent learning and deficits in hippocampal synaptic plasticity that appears to be critical in learning and memory (Tecott et al., 1998, Proc. Natl. Acad. Sci. 95:15026-15031). Thus 5-HT2C receptor knockouts may replicate some of the cognitive deficits found in PWS. 5-HT2CR knockout mice therefore share many, but not all (e.g., failure to thrive, which may be mediated by HBII-85 (Ding et al., 2005, Mamm. Genome 16:424-431)), critical phenotypes with PWS patients.

AMPA Receptor: Excitotoxicity, Seizure, and Amyotrophic Lateral Sclerosis (ALS)

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as AMPA receptor, AMPAR, or quisqualate receptor) is a non-NMDA-type ionotropic transmembrane receptor for glutamate in the central nervous system (CNS). Postsynaptic ion channels activated by glutamate include NMDA (N-methyl-D-aspartic acid)-type glutamate channels, which are highly Ca^{2+} permeable, and AMPA-type glutamate channels, which mediate the majority of rapid excitatory neurotransmission. AMPA channels are homo- or hetero-oligomeric assemblies composed of various combinations of four possible subunits, GluR1, GluR2, GluR3 and GluR4. The Ca^{2+} conductance of AMPA receptors differs markedly according to whether the GluR2 subunit is present or not and whether it has undergone post-transcriptional RNA editing at the Q/R site. AMPA receptors that contain at least one Q/R edited GluR2 subunit are Ca^{2+} impermeable. These properties of GluR2 are generated by RNA editing at the Q/R site in the putative second transmembrane domain (M2), during which a glutamine (Q) codon is replaced by an arginine (R) codon (Seeburg et al., 2001, Brain Res. 907:233-243). It is thought that arginine in the pore of the channel impedes Ca^{2+} permeation. Analyses of adult rat, mouse, and human brains have demonstrated that almost all GluR2 mRNA in neurons is edited. In contrast, the Q/R site of GluR1, GluR3 and GluR4 subunits are always unedited, and glutamine remains at this crucial position. Therefore, AMPA receptors lacking a Q/R edited GluR2 subunit or lacking GluR2 altogether are highly Ca^{2+} permeable (Kawahara and Kwak, 2005, ALS Other Motor Neuron Disord 6:131-144; Seeburg et al., 2001, Brain Res. 907:233-243).

Alternative splicing of the GluRs plays a critical role in AMPA receptor physiology, influencing sensitivity to glutamate, kinetics of channel desensitization, and intracellular trafficking. Two specific alternatively spliced variants of all GluRs called "flip" and "flop" are normally expressed in the CNS. These consist of 115 base pair exons that constitute the flip/flop cassette (Sommer et al., 1990, Science 249:1580-1585) and encode part of the extracellular segment that precedes the fourth transmembrane domain. This domain appears to modulate receptor desensitization and channel conductance (Mosbacher et al., 1994, Science 266:1059-1062). Generally, the AMPA "flip" variants are resistant to desensitization, whereas the "flop" variants are readily desensitized, although the kinetic difference depends on the subunit and, for heteromeric channels, on subunit compositions (Grosskreutz et al., 2003, Eur. J. Neurosci. 17:1173-1178; Koike et al., 2000, J. Neurosci. 25:199-207; Mosbacher et al., 1994; Sommer et al., 1990, Science 249:1580-1585). The extracellular flip/flop region may also interact with ER luminal proteins to regulate trafficking of AMPA receptors, with flip isoforms inserted into the cell membrane and flop isoforms trapped internally (Coleman et al., 2006, J. Neurosci. 26:11220-11229), although this has yet to be confirmed in neurons. Together these data show that when flip/flop ratio of GluR1, GluR3 and GluR4 is elevated, neurons are more excitable and show greater Ca^{2+} conductance.

In motor neurons (MNs) it has been consistently demonstrated that AMPA receptor desensitization significantly impacts the shape of the glutamatergic synaptic response, as well as robustly regulating network activity (Ballerini et al., 1995, Eur. J. Neurosci. 7:1229-1234; Funk et al., 1995, J. Neurosci. 15:4046-4056). In addition, studies in several different brain regions have found that AMPA receptor desensitization has potent effects on baseline evoked and spontaneous synaptic events (Akopian and Walsh, 2007, J. Physiol. 580:225-240; Atassi and Glavinovic, 1999, Pflugers Arch. 437:471-478; Xia et al., 2005, J. Pharmacol. Exp. Ther. 313:277-285), although this is controversial, especially in hippocampus (Arai and Lynch, 1998, Brain Res. 799:230-234; Hjelmstad et al., 1999, J. Neurophysiol. 81:3096-3099). Further, AMPA receptor desensitization has been shown to be critical in shaping the synaptic response under conditions of higher frequency activity by strongly regulating synaptic integration (Arai and Lynch, 1998, Brain Res. 799:235-234; Chen et al., 2002, Neuron 33:779-788). Prolonging AMPA channel desensitization can also generate excessive network synchronization, leading to paroxysmal bursting that may interfere with normal network function (Funk et al., 1995, J. Neurosci. 15:4046-4056; Pelletier and Hablitz, 1994, J. J. Neurophysiol. 72:1032-1036; Qiu et al., 2008, J. Neurosci. 28:3567-3576). Thus, it is not surprising that reducing AMPA receptor desensitization profoundly increases excitotoxicity induced by glutamate and AMPA.

In spinal MNs, as well as in hippocampus and cerebellar granule cells, treatment with AMPA alone does not induce neurotoxicity. However, AMPA combined with cyclothiazide, which greatly reduces AMPA receptor desensitization, leads to neuronal cell death (Carriedo et al., 2000, J. Neurosci. 20:240-250; May and Robison, 1993, J. Neuroschem. 60:1171-1174; Puia et al., 2000, Prog. Neuropsychopharm. Biol. Psychiatr. 24:1007-1015). AMPA-mediated neurotoxicity is also amplified by cyclothiazide in cerebellar purkinje cells (Brorson et al., 1995, J. Neurosci. 15:4515-4524) and cortical neurons (Jensen et al., 1998, Neurochem. Int. 32:505-513). Further, in HEK293 cells, AMPA induces excitotoxicity when flip but not flop GluR isoforms are expressed (fizuka et al., 2000, Eur. J. Neurosci. 12:3900-3908). AMPA receptor desensitization can also protect against NMDA receptor mediated excitotoxicity (Jensen et al., 1998, Neurochem. Int. 32:505-513; Zorumski et al., 1990, Neuron 5:61-66). Finally, decreases in AMPA receptor desensitization have been proposed to play a role in excitotoxicity after traumatic brain injury (Goforth et al., 1999, J. Neurosci. 19:7367-7374). Thus, AMPA receptor desensitization plays a critical role in normal neuronal function and excitotoxicity.

Emerging evidence supports the idea that Ca^{2+}-permeable AMPA channels, which are highly expressed on MNs, are key contributors to injury of MNs in amyotrophic lateral sclerosis (ALS) (Corona et al., 2007, Expert Opin. Ther. Targets 11:1415-1428; Van Den et al., 2006, Biochem. Biophys. Acta. 1762:1068-1082). Compared to most cell types, MNs have relatively poor capacity to buffer Ca^{2+}, due to reduced levels of Ca^{2+} binding proteins including calbindin and parvalbumin (Alexianu et al., 1994, Ann. Neurol. 36:846-858; Ince et al., 1993, Neuropathol. Appl. Neurobiol. 19:291-299;

Palecek et al., 1999, J. Physiol. 520 pt 2: 485-502). It appears that spinal MNs of ALS mice have even fewer of these Ca^{2+}-binding proteins (Siklos et al., 1998, J. Neuropathol. Exp. Neurol. 57:571-587). Amplifying that point, recent studies have shown that G93A ALS mice interbred with mice overexpressing parvalbumin showed a delayed onset of motor disease (Beers et al., 2001, J. Neurochem. 79:499-509). According to a speculative model of glutamate-mediated excitotoxicity involving AMPA channels in ALS, Ca^{2+} influx through Ca^{2+}-permeable AMPA channels is not adequately buffered in MNs and ends up accumulating in mitochondria. High Ca^{2+} is toxic to mitochondria, causing generation of apoptotic mediators such as ROS and cytochrome c, as well as opening of a permeability transition pore through which apoptotic mediators are released. It is thought that these mitochondrial factors are released from MNs and exert deleterious effects on glutamate transporters on adjacent astrocytes. Astrocytic glutamate transporters are responsible for taking up synaptic glutamate, and when they are compromised, glutamate accumulates in the synaptic region. The glutamate transporter with the most functional significance in this context is EAAT2/GLT-1, as it is widely expressed in astrocytes throughout the CNS and as it has the highest affinity for glutamate. In over ~65% of ALS cases, and in ALS mice, EAAT2 activity in the cortex and spinal cord is compromised (Van Den et al., 2006, Biochem. Biophys. Acta. 1762:1068-1082). Thus, in this model, increased glutamate then further stimulates more Ca^{2+} influx though AMPA channels causing a feed-forward cycle that ultimately leads to too much Ca^{2+} in MNs. This sets into motion a cascade that leads by unknown mechanisms to MN cell death.

There is also evidence that decreased desensitization of AMPA channels, due to increased flip/flop expression ratio, may exacerbate glutamate excitotoxicity in ALS. In spinal MNs of ALS subjects, the level of the AMPA receptor flip variants was found to be significantly elevated relative to that of the flop isoforms (Tomiyama et al., 2002, Synapse 45:245-249). Although this work from a highly published neuroanatomy group is the only study thus far to examine flip/flop isoforms in spinal cord of ALS patients, the findings were quite compelling. They observed a 41-66% decrease in the flop isoforms of GluR1-3 only in the ventral horn (layer IX), where MN soma are localized. Further, they provided evidence that their transcript labeling was restricted to MN soma. Unfortunately, flip/flop protein levels were not examined, since specific antibodies for flip and flop isoforms of GluRs do not exist. A remarkably similar change in AMPA receptor flip/flop ratios was independently observed in MNs from G93A SOD 1 ALS mice (Spalloni et al., 2004, Neurobiol. Dis. 15:340-350). This study showed increased flip isoforms, especially GluR3 and GluR4, and thus dramatic increases in flip to flop ratios. Interestingly, these changes were specific to mice overexpressing mutant SOD1 but were not found in mice overexpressing normal human SOD1. Further, electrophysiological studies demonstrated reduced desensitization of AMPA currents in MNs of G93A transgenics compared to control and SOD1 transgenics, as well as robust increases in blockade of desensitization by cyclothiazide. Both of these properties are characteristic of increased flip isoforms (Partin et al., 1994, Mol. Pharm. 46:129-138; Sommer et al., 1990, Science 249:1580-1585). In addition, spontaneous glutamatergic synaptic events are prolonged due to increased decay times in MNs of G93A ALS mice compared to control and SOD1 transgenics, also consistent with an increase in flip isoforms (Pieri et al., 2003, Neurosci. 122:47-58). Together, these studies indicate that aberrant flip-flop ratios are present in MNs of ALS individuals, and that these changes are replicated in a mouse model of the disease. These data strongly implicate a contribution of aberrant flip-flop levels of AMPA channels to MN excitotoxicity in ALS. Specifically, MNs with high levels of Ca^{2+}-permable AMPA receptors (Kawahara et al., 2004, Nature 427:801), and especially membrane bound non-desensitizable flip isoforms, permit enhanced postsynaptic Ca^{2+} influx in response to a given glutamate load (FIG. **2**).

Increases in the flip to flop ratio in adult hippocampus have also been reported after seizures. This recapitulation of the immature phenotype after seizures is seen for many other neurotransmitter related proteins (Brooks-Kayal et al., 1998). In rat hippocampus, the flip variant of both GluR1 and GluR2 is increased after seizures induced by tetanus toxin (Rosa et al., 1999, Epilepsy Res. 36:243-251) and kindling (Kamphuis et al., 1992, Neurosci. Lett. 148:51-54; Kamphuis et al., 1994, nature 448:39-43). In hippocampal tissue from humans with epilepsy, increases in flip-flop ratios have also been reported. The GluR1 flip variant is increased in hippocampal astrocytes, as assessed both functionally with electrophysiology and at the transcript level with single-cell real time PCR (Seifert et al., 2004, J. Neurosci. 24:1996-2003). In hippocampal neurons, expression of the GluR1 flip variant is increased in CA1 after seizures (Eastwood et al., 1994, Neuroreport 5:1325-1328; de Lanerolle et al., 1998, Eur. J. Neurosci. 10:1687-1703). While the flop variant is found in CA3 and dentate in non-epileptic hippocampus (Eastwood et al., 1994, Neuroreport 5:1325-1328), in tissue from patients with TLE the flop variant of GluR1 is found only in the dentate (de Lanerolle et al., 1998, Eur. J. Neurosci. 10:1687-1703). Thus flop appears to be downregulated in CA3 in epileptic hippocampus. The increase in flip to flop ratios in epileptic hippocampus would increase synaptic gain and could contribute to post-seizure hyperexcitability.

Aph1B: Alzheimer's Disease

Alzheimer's Disease (AD) is a common neurodegenerative disorder and results in a severe decline in cognition, and ultimately dementia, especially in the aged population. Progression of the disease is linked to the characteristic deposition of β-amyloid and tau neurofibrillary tangles (NTs).

Compelling evidence shows that amyloid-beta peptide (Aβ) contributes to the etiology of AD. Aβ is a 38-43 amino acid peptide that is produced in neurons by the sequential proteolytic cleavage of APP by β-secretase and γ-secretase, the latter step yielding isoforms Aβ40 and Aβ42. Aβ42 appears to be the most highly amyloidogenic isoform. In humans, γ-secretase complexes are heterogeneous, comprised of two presenilin genes (PS1 and PS2), along with Aph1A (long or short isoforms) and Aph1B (Shirotani et al., 2004, J. Biol. Chem. 279:41340-41345).

Gamma-secretase is a tri-partite protein complex composed of presenilin, nicastrin, and ApH1. ApH1 is composed of both Aph1A and Aph1B. Transgenic elimination of Aph1B blocked the processing of amyloid precursor protein (APP) to A-beta, but did not effect the processing of other non-amyloidal substrates (Serneels et al., 2009, Science 324:639-642).

A common understanding about AD is that APP processing sequentially by BACE then gamma-secretase, results in the production of Abeta42 among other isoforms. The Abeta42 isoform, which is the direct product of gamma-secretase cleavage is thought to be especially harmful, first as a soluble factor that impairs cognition and later in the production of amyloid plaques that may further enhance disease progression. Therefore, an intense search for compounds that reduce the activity of gamma-secretase is underway. Unfortunately, in addition to actively cleaving APP, gamma-secretase also cleaves a number of other important non-amyloidal substrates, such as Notch. Thus, there is an urgent need for improved compounds that significantly reduce gamma-secretase production of Aβ-42 in the brain, without affecting its cleavage of other non-APP substrates.

O-GlcNAcase (OGA): Alzheimer's Disease

Levels of N-acetyl-D-glucosamine (O-GlcNAc) modification of proteins are known to be reduced throughout the brains of Alzheimer's Disease (AD) patients due to low glucose availability, and this global alteration is thought to be pathological in AD progression (Fischer, 2008, Nature Chem. Biol. 4:448-449). Dynamic cycling of O-GlcNAc is regulated by addition through N-acetyl-D-glucosamine polypeptidyltransferase (OGT) and removal by O-GlcNAcase (OGA). Removal of O-GlcNAc from proteins by OGA may be involved in controlling multiple cellular pathways. OGA has been shown to mediate transcriptional activation both by directly modifying the transcriptome and by preventing the recycling of transcription factors in the nucleus (Bowe et al., 2006, Mol. Cell. Biol. 26:8539-8550). Additionally, OGA has been implicated in chromatin remodeling and transcriptional repression via interactions with OGT/histone deacetylase (HDAC) complexes and or C-terminal histone acetyltransferase (HAT) activity (Lazarus et al., 2009, Int. J. Biochem. Cell Biol. 41:2134-2146; Whisenhunt et al., 2006, Glycobiol. 16:551-563). There is also evidence that phosphorylation and O-GlcNAcylation exist in dynamic equilibrium. Serine/threonine residues that otherwise may be phosphorylated by serine/threonine kinases can be instead O-GlcNAc modified, as is the case with tau (Yuzwa et al., 2008, Nat. Chem. Biol. 4:483-490). Further evidence indicates that O-GlcNAcylation of tau can cause trafficking and retention of tau in the nucleus (Guinez et al., 2005, Int. J. Biochem. Cell Biol. 37:765-774) Importantly to AD pathology, low levels of O-GlcNAc on tau may allow for tau hyperphosphorylation, which leads to neurofibrillary tangle (NT) formation. Thus alteration of brain glycosylation will have effects on multiple pathways.

HER3: Cancer

About 25% of breast cancers involve overexpression of the HER2, with highly aggressive metastasis, and poor clinical prognosis. Herceptin shows some success against HER2 overexpressing breast cancer cells (HOBCsa), and tyrosine kinase inhibitors (TKIs) have shown promise in early clinical trials. However, HOBCs show remarkable acquired resistance to current drugs. Recent studies have shown HER3 is overexpressed in HOBCs and exerts a critical role in tumorogenesis, metastasis, and acquisition of resistance to TKIs (Baselga, J. & Swain, S. M. (2009) Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 9:463-475). For EGFRs, dimerization and transactivation by tyrosine kinase is essential for signaling activity. Although HER3 lacks intrinsic tyrosine kinase activity, the most potent EGFR activated dimers are heterodimers between HER2 and HER3, leading to potent HER3-mediated TKI resistance via activation of the PI3K-Akt pathway (Baselga et al., 2009, Nat Rev Cancer 9:463-475). Since the loss of HER3 function ameliorates the transforming capabilities of HER2, there is a pressing need for new drugs against HER3 for treating breast cancer.

Forkhead Box Protein M1 (FOXM1): Anti-Tumor

Forkhead box protein M1 (FOXM1) is a protein that is encoded by the FOX1 gene and is a member of the FOX family of transcription factors. FOXM1 is known to play a key role in cell cycle progression. There are three FOXM1 isoforms, A, B and C. Isoform FOXM1A has been shown to be a gene transcriptional repressor whereas the remaining isoforms (B and C) are both transcriptional activators. Hence, it is not surprising that FOXM1B and C isoforms have been found to be upregulated in human cancers (Wiestra et al., 2007, Biol. Chem. 388 (12): 1257-74.

The exact mechanism of FOXM1 in cancer formation remains unknown. It is thought that upregulation of FOXM1 promotes oncogenesis through abnormal impact on its multiple roles in cell cycle and chromosomal/genomic maintenance. FOXM1 overexpression is involved in early events of carcinogenesis

FOXM1 gene is now known as a human proto-oncogene. Abnormal FOXM1 upregulation was subsequently found in the majority of solid human cancers including liver (The et al., 2002, Cancer Res. 62: 4773-80) breast (Wonsey et al., 2005, Cancer Res. 65 (12): 5181-9), lung (Kim et al., 2006, Cancer Res. 66 (4): 2153-61), prostate (Kalin et al., 2006, Cancer Res. 66 (3): 1712-20; cervix of uterus (Chan et al., 2008, J. Pathol. 215 (3): 245-52), colon (Douard et al., 2006, Surgery 139 (5): 665-70), pancreas (Wang et al., 2007, Cancer Res. 67 (17): 8293-300), and brain (Liu et al., 2006, Cancer Res. 66 (7): 3593-602).

Cyclophilin D: ALS, Hepatitis B Viral Infection, and Liver Cancer

Cyclophilin D (CypD) is a protein located in the matrix of the mitochondria, and is one of the components of the mitochondrial permeability transition pore (MPTP). Under conditions of oxidative stress, the MPTP becomes extremely permeable to the influx of calcium ions, therein causing mitochondrial swelling eventually leading to cell apoptosis. Targeting the MPTP/CypD complex in hepatitis B virus (HBV) infected hepatocytes using the non-specific CypD inhibitor, Cyclosporin A, inhibits HBV replication (Waldemeier et al., 2003, Current Medicinal Chemistry 10:1485-1506). In addition, when used in patients with neurodegerative diseases, Cyclosporin A exhibits cytoprotective effects by way of blocking the opening of the MPTP. Although shown to be efficacious, Cyclosporin A is an immunosuppressive drug, and can also bind non-specifically to other cyclophilins, therefore causing off-target effects. Inhibition of CypD expression using siRNA has been examined as a potential cardioprotective therapy (Kato et al., 2009, Cardiovasc. Res. 83:335-344). However SMOs have a therapeutic advantage over siRNA in that unlike siRNA, SMOs do not affect transcript degradation through recruitment of RNAase H which can cause immune reactions and other off target effects.

There is presently no known cure for PWS, ALS, AD or any of a number of other diseases that result from aberrant pre-mRNA splicing. There is a need in the art for the development of more selective and efficacious therapeutic agents for the treatments of various diseases and conditions affected or mediated by 5HT2CR, GluRs, OGA, Aph1B, FOXM1, ERBB3, and CypD. In addition, there are a number of diseases where altering pre-mRNA splicing may have a positive therapeutic effect even when that gene is not directly affected by the pathogenesis of the disease. Accordingly, there is an urgent need in the art for compositions and methods related to pre-mRNA splicing as it affects various diseases and disorders. The present invention fills this need.

SUMMARY OF THE INVENTION

In one embodiment, the present invention comprises a method of modulating splicing of a pre-mRNA, the method comprising contacting a cell with an effective amount of a splice modulating oligonucleotide (SMO), where the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA. In one aspect, the resulting mRNA encodes a protein selected from the group consisting of a glutamate activated AMPA receptor subunit (GluR), OGA, Aph1B, FOXM1, HER3, and CypD. In another aspect, the GluR is selected from the group consisting of GluR1, GluR2, GluR3, GluR4 and any combination thereof.

In another embodiment, the present invention comprises a method of modulating splicing of a pre-mRNA, the method comprising contacting a cell with an effective amount of a splice modulating oligonucleotide (SMO), where the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice suppressor (ESS) site, and an intronic splice suppressor (ISS) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is included in the resulting mRNA. In one aspect, the resulting mRNA encodes a 5-HT2C receptor.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with a 5-HT2CR splicing defect, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA, where when the SMO specifically binds to the complementary sequence, exon 5b is included in the resulting mRNA encoding a full-length, functional 5-HT2C receptor, and where the SMO increases expression of a full-length, functional 5-HT2C receptor in the subject and treats the subject afflicted with a 5-HT2CR splicing defect. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1-56.

In another embodiment, the present invention comprises a method of treating a subject afflicted with Prader-Willi Syndrome (PWS), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA, where when the SMO specifically binds to the complementary sequence, exon 5b is included in the resulting mRNA encoding a full-length, functional 5-HT2C receptor, and where the SMO increases expression of the full-length, functional 5-HT2C receptor in the subject and treats the subject afflicted with PWS. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1-56.

In yet another embodiment, the present invention comprises, a method of treating a subject afflicted with hyperphagia, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA, where when the SMO specifically binds to the complementary sequence, exon 5b is included in the resulting mRNA encoding a full-length, functional 5-HT2C receptor, and where the SMO increases expression of the full-length, functional 5-HT2C receptor in the subject and treats the subject afflicted with hyperphagia. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1-56.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with symptoms of obsessive-compulsive disorder, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA, where when the SMO specifically binds to the complementary sequence, exon 5b is included in the resulting mRNA encoding a full-length, functional 5-HT2C receptor, and where the SMO increases expression of the full-length, functional 5-HT2C receptor in the subject and treats the subject afflicted with symptoms of obsessive-compulsive disorder. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1-56.

In another embodiment, the present invention comprises a method of increasing expression of a transmembrane neuronal receptor in a subject, the method comprising contacting a cell with an effective amount of a splice modulating oligonucleotide (SMO), where the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of an intron-exon splice site, an exonic splice suppressor (ESS) site, and an intronic splice suppressor (ISS) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is included in the resulting mRNA encoding a full-length, functional transmembrane neuronal receptor, and where the SMO increases expression of the full-length, functional transmembrane neuronal receptor. In one aspect, the transmembrane neuronal receptor is a 5-HT2C receptor. In another aspect, the subject is afflicted with a disease or disorder selected from the group consisting of PWS, Angelman Syndrome, hyperphagia induced obesity, obsessive/compulsive disorder, depression, psychotic depression, major depressive disorder, bipolar disorder, sleep impairment, autism, schizophrenia, Parkinson's disease, drug addiction, spinal cord injury, traumatic brain injury, neuropathic pain, diabetes, and Alzheimer's disease.

In still another embodiment, the present invention comprises a method of increasing expression of a transmembrane neuronal receptor in a subject, the method comprising contacting a cell with an effective amount of a splice modulating oligonucleotide (SMO), where the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA encoding the transmembrane neuronal receptor, and where the SMO increases expression of the transmembrane neuronal receptor. In one aspect, the transmembrane neuron receptor is a glutamate activated AMPA receptor subunit (GluR) selected from the group consisting of GluR1, GluR2, GluR3, GluR4, and any combination thereof.

In another embodiment, the present invention comprises a method of treating a subject afflicted with amyotrophic lateral sclerosis (ALS), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA encoding a GluR, where the GluR is selected from the list consisting of GluR1, GluR2, GluR3, GluR4, and any combination thereof, where the SMO decreases expression of the flip isoform of the GluR in the subject and treats the subject afflicted with ALS. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 57-526.

In yet another embodiment, the present invention comprises a method of treating a subject afflicted with epilepsy the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA encoding a GluR, where the GluR is selected from the list consisting of GluR1, GluR2, GluR3, GluR4, and any combination thereof, where the SMO decreases expression of the flip isoform of the GluR in the subject and treats the subject afflicted with epilepsy. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 57-526.

In another embodiment, the present invention comprises a method of treating a subject afflicted with Alzheimer's Disease (AD), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 8 of the mRNA encoding O-GlcNAcase (OGA), where the SMO increases expression of OGAΔ8 in the subject and treats the subject afflicted with AD. In one aspect the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 527-611.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with Alzheimer's Disease (AD), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of an intron-exon splice site, an exonic splice suppressor (ESS) site, and an intronic splice suppressor (ISS) site, where when the SMO specifically binds to the complementary sequence, the intron adjacent to the intron-exon boundary is included in the resulting mRNA, where the intron is intron 10 of the mRNA encoding O-GlcNAcase (OGA), and where the SMO increases expression of a truncated OGA protein (OGA10t) in the subject and treats the subject afflicted with AD. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 612-661.

In another embodiment, the present invention comprises a method of treating a subject afflicted with Alzheimer's Disease (AD), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 4 of the mRNA encoding Aph1B, where the SMO increases expression of Aph1BΔ4 in the subject and treats the subject afflicted with AD. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 662-728.

In yet another embodiment, the preset invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 3 of the mRNA encoding HER3, and where the SMO increases expression of a HER3Δ3 in the subject and treats the subject afflicted with cancer. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 729-802. In another aspect, the cancer is selected from the group consisting of breast cancer, liver cancer, lung cancer, prostate cancer, cervical cancer, colon cancer, pancreatic cancer, and brain cancer.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice suppressor (ESS) site, and an intronic splice suppressor (ISS) site, where when the SMO specifically binds to the complementary sequence, the intron adjacent to the intron-exon boundary is included in the resulting mRNA, where the intron is intron 3 of the mRNA encoding HER3, and where the SMO increases expression of a truncated HER3 protein in the subject and treats the subject afflicted with cancer. In one aspect, the method of claim **32**, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 729-802. In another aspect, the cancer is selected from the group consisting of breast cancer, liver cancer, lung cancer, prostate cancer, cervical cancer, colon cancer, pancreatic cancer, and brain cancer.

In another embodiment, the present invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 11 of the mRNA encoding HER3, and where the SMO increases expression of a HER3Δ11 in the subject and treats the subject afflicted with cancer. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 803-813. In another aspect, the cancer is selected from the group consisting of a breast cancer, liver cancer, lung cancer, prostate cancer, cervical cancer, colon cancer, pancreatic cancer, and brain cancer.

In yet another embodiment, the present invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA encoding FOXM1, and where the SMO increases expression of a FOXM1Δ3 or FOXM1Δ6 in the subject and treats the subject afflicted with cancer. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 919-1090.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with a hepatitis B virus (HBV) infection, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 1 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ1 in the subject and treats the subject afflicted with an HBV infection. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 814-857.

In yet another embodiment, the present invention comprises a method of treating a subject afflicted with a hepatitis B virus (HBV) infection, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 3 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ3 in subject and treats the subject afflicted with an HBV infection. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 858-918.

In another embodiment, the present invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 1 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ1 in the subject and treats the subject afflicted with cancer. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 814-857. In another aspect, the cancer is a liver cancer.

In still another embodiment, the present invention comprises a method of treating a subject afflicted with a cancer, the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective

amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 3 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ3 in the subject and treats the subject afflicted with cancer. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 858-918. In another aspect, the cancer is a liver cancer.

In yet another embodiment, the present invention comprises a method of treating a subject afflicted with amyotrophic lateral sclerosis (ALS), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 1 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ1 in the subject and treats the subject afflicted with ALS. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 814-857.

In another embodiment, the present invention comprises a method of treating a subject afflicted with amyotrophic lateral sclerosis (ALS), the method comprising administering a splice modulating oligonucleotide (SMO) to the subject, where an effective amount of the SMO contacts a cell so that the SMO specifically binds to a complementary sequence on a pre-mRNA in at least one of the group consisting of an intron-exon splice site, an exonic splice enhancer (ESE) site, and an intronic splice enhancer (ISE) site, where when the SMO specifically binds to the complementary sequence, the exon adjacent to the intron-exon boundary is excluded from the resulting mRNA, where the exon is exon 3 of the mRNA encoding CypD, and where the SMO increases expression of a CypDΔ3 in the subject and treats the subject afflicted with ALS. In one aspect, the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 858-918. In another aspect, the isolated nucleic acid selected from the group consisting of SEQ ID NOs. 1-1090.

In one embodiment, the present invention comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a 5HT2CR, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 1-56.

In still another embodiment, the present invention comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a GluR, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 57-526.

In yet another embodiment, the present invention comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a OGA, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 527-661.

In another embodiment, the present invention comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a Aph1B, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 662-728.

In still another embodiment, the present invention a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a HER3, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 729-813.

In yet another embodiment, the present invention also comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a CypD, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 814-918.

In another embodiment, the present invention comprises a pharmaceutical composition comprising a splice modulating oligonucleotide (SMO) that targets a pre-mRNA that matures to a FOXM1, where the SMO is an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs. 919-1090.

BRIEF DESCRIPTION OF THE DRAWINGS

For the purpose of illustrating the invention, there are depicted in the drawings certain embodiments of the invention. However, the invention is not limited to the precise arrangements and instrumentalities of the embodiments depicted in the drawings.

FIG. **1**, comprising FIG. **1**A through FIG. **1**I, is a series of images depicting splice modulating oligonucleotide (SMO) mediated induction of full-length survival motor neuron protein (SMN) expression and concomitant phenotypic improvement in spinal muscular atrophy (SMA) mice. FIG. **1**A depicts a photomicrograph of brain section in an uninjected control. FIG. **1**B depicts SMO fluorescent label broadly distributed throughout brain regions 24 hours following bilateral intracerebroventricular (ICV) injection of the SMO. FIG. **1**C is a higher magnification of the area within the box in FIG. **1**B. FIG. **1**D through FIG. **1**I depict results obtained from SMA mice (N=5), injected with 1 μg SMO (per ventricle) on postnatal day 1, 3, 5, 7, 10, and harvested on day 12, and compared with uninjected controls (N=9). FIG. **1**D depicts the results of real-time PCR of brain sections taken at the level of hippocampus shows full-length SMN expression was increased in SMA mice following Icy injections of SMO. FIG. **1**E and FIG. **1**F depict Western analysis of brain sections taken at the level of hippocampus (FIG. **1**E) and cervical spinal cord (FIG. **1**F) showing SMN expression increases in SMA mice following ICV injections of SMO. FIG. **1**G is a graph depicting SMN expression measured by Westerns as significantly increased in brain and spinal cord of SMO-treated SMA mice when measured as a percentage of wild-type controls. FIG. **1**H is a graph depicting body weight of SMA mice which was significantly increased relative to uninjected controls at P12 following ICV injections of SMO ($P<0.01$). FIG. **1**I is a graph depicting SMO-treated SMA mice with significant improvement in righting response at P12 compared to untreated controls. In total, all 5 SMO-treated mice could right themselves from at least one side, while only 3 of 9 untreated mice could accomplish this task. However, motor function was not fully restored as most SMO-treated and untreated SMA mice could not right themselves from both sides.

FIG. **2** is a schematic illustration depicting alternative splicing at the flip-flop cassette exons of glutamate receptor (GluR) subunits of AMPA receptors. Alternative splicing of mutually exclusive flip and flop exons of GluR1-4 leads to either flip exon-containing or flop-exon-containing transcripts. Co-skipping of both flip and flop exons results in out-of-frame transcripts that are truncated and unstable.

FIG. **3** depicts a ClustalW alignment of flip and flop exons of mouse GluR1-4. Dark shading indicates positions of complete identity, while lighter shading shows divergence. The sequences compared are as follows: mGluR1-flop exon (SEQ ID NO: 1090); mGluR2-flop exon (SEQ ID NO: 1091); mGluR3-flop exon (SEQ ID NO: 1092); mGluR4-flop exon (SEQ ID NO: 1093); mGluR1-flip exon (SEQ ID NO: 1094); mGluR2-flip exon (SEQ ID NO: 1095); mGluR3-flip exon (SEQ ID NO: 1096); and mGluR4-flip exon (SEQ ID NO: 1097).

FIG. **4** is a schematic illustration of candidate SMOs evaluated for skipping GluR3 flip exon. All SMO-target pairs have favorable thermodynamic properties and are complementary to splice sites and/or ESEs. The GluR3 flip exon, and adjoining intron nucleotides, is reflected in the fourth line of FIG. **4** (SEQ ID NO: 1101). The GluR4 flip exon, and adjoining intron nucleotides, is reflected in the first line of FIG. **4** (SEQ ID NO: 1098), showing only nucleotides differing from SEQ ID NO: 1101. The GluR1 flip exon, and adjoining intron nucleotides, is reflected in the second line of FIG. **4** (SEQ ID NO: 1099), showing only nucleotides differing from SEQ ID NO: 1101. The GluR2 flip exon, and adjoining intron nucleotides, is reflected in the third line of FIG. **4** (SEQ ID NO: 1100), showing only nucleotides differing from SEQ ID NO: 1101.

FIG. **4** also reflects the proposed top 5 antisense oligonucleotides in the bottom two lines of the figure. From left to right and top to bottom, SEQ ID NO: 123, SEQ ID NO: 1102, SEQ ID NO: 1103, SEQ ID NO: 1104, and SEQ ID NO: 1105.

FIG. **5** is a schematic illustration of candidate SMOs evaluated for skipping GluR2 exon 15 (flip). All SMO-target pairs have favorable thermodynamic properties and are complementary to splice sites and/or ESEs. The GluR2 exon 15 (flip), and adjoining intron nucleotides, is reflected in the first line of FIG. **5** (SEQ ID NO: 1106). The candidate SMOs follow below in the following order: SEQ ID NO: 433, SEQ ID NO: 442, SEQ ID NO: 443, SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 404, SEQ ID NO: 1107, SEQ ID NO: 1108 (aligned center), SEQ ID NO: 1109 (aligned right), SEQ ID NO: 1110 (aligned right), SEQ ID NO: 1111, SEQ ID NO: 412, SEQ ID NO: 441, SEQ ID NO: 1112, SEQ ID NO: 453, SEQ ID NO: 452, SEQ ID NO: 451, SEQ ID NO: 449, SEQ ID NO: 463, and SEQ ID NO: 1113 (aligned right).

FIG. **6** is a graph depicting the relative expression of GluR1, GluR2, GluR3 and GluR4 flip and flop isoforms following ICV injections of SMOs targeting GluR1-flip and GluR3-flip isoforms.

FIG. **7** is a graph depicting the relative change in expression of GluR1, GluR2, Glur3 and GluR4 flip and flop isoforms following ICV injections of SMOs targeting all four GluR flip isoforms.

FIG. **8** is a graph depicting the effect of ICV administration of a SMO targeting GluR-1 on seizure activity in mice.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to splice modulating oligonucleotides (SMOs) affecting splicing of pre-mRNA expressed from various genes. In one embodiment, the instant invention provides compositions and methods for correcting aberrant splicing of pre-mRNA that results in a defective protein and consequently causes a disease or a disorder in a subject, wherein the subject is preferably human.

In another embodiment, the instant invention provides compositions and methods for treating a human disease or disorder by modulating pre-mRNA splicing of a nucleic acid even when that nucleic acid is not aberrantly spliced in the pathogenesis of the disease or disorder being treated.

In one embodiment, the human disease or disorder is neurological. In another embodiment, the human disease is a cancer.

Definitions:

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and nucleic acid chemistry and hybridization are those well known and commonly employed in the art.

Standard techniques are used for nucleic acid and peptide synthesis. The techniques and procedures are generally performed according to conventional methods in the art and various general references (e.g., Sambrook and Russell, 2001, Molecular Cloning, A Laboratory Approach, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., and Ausubel et al., 2002, Current Protocols in Molecular Biology, John Wiley & Sons, NY), which are provided throughout this document.

The nomenclature used herein and the laboratory procedures used in analytical chemistry and organic syntheses described below are those well known and commonly employed in the art. Standard techniques or modifications thereof, are used for chemical syntheses and chemical analyses.

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used.

"Antisense" refers particularly to the nucleic acid sequence of the non-coding strand of a double stranded DNA molecule encoding a protein, or to a sequence which is substantially homologous to the non-coding strand. As defined herein, an antisense sequence is complementary to the sequence of a double stranded DNA molecule encoding a protein. It is not necessary that the antisense sequence be complementary solely to the coding portion of the coding strand of the DNA molecule. The antisense sequence may be complementary to regulatory sequences specified on the coding strand of a DNA molecule encoding a protein, which regulatory sequences control expression of the coding sequences.

By the term "applicator," as the term is used herein, is meant any device including, but not limited to, a hypodermic syringe, a pipette, and the like, for administering the compounds and compositions of the invention.

"Complementary" as used herein refers to the broad concept of subunit sequence complementarity between two nucleic acids, e.g., two DNA molecules. When a nucleotide position in both of the molecules is occupied by nucleotides normally capable of base pairing with each other, then the nucleic acids are considered to be complementary to each other at this position. Thus, two nucleic acids are substantially complementary to each other when at least about 50%, preferably at least about 60% and more preferably at least about 80% of corresponding positions in each of the molecules are occupied by nucleotides which normally base pair with each other (e.g., A:T and G:C nucleotide pairs).

A "disease" is a state of health of subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject's health continues to deteriorate. In contrast, a "disorder" in an subject is a state of health in which the subject is able to maintain homeostasis, but in which the subject's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the subject's state of health. In preferred embodiments, the subject is an animal. In more preferred embodiments, the subject is a mammal. In most preferred embodiments, the subject is a human.

A disease or disorder is "alleviated" if the severity of a symptom of the disease or disorder, or the frequency with which such a symptom is experienced by a subject, or both, are reduced.

The terms "effective amount" and "pharmaceutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease or disorder, or any other desired alteration of a biological system. An appropriate effective amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

As used herein, the term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" as used herein is defined as the transcription and/or translation of a particular nucleotide sequence.

The term "exonic regulatory elements" as used herein refers to sequences present on pre-mRNA that enhance or suppress splicing of an exon. An exonic regulatory element that enhances splicing of an exon is an exonic splicing enhancer (ESE). An exonic regulatory element that suppresses splicing of an exon is an exonic splicing suppressor (ESS). An intronic regulatory element that enhances splicing of an exon is an intronic splicing enhancer (ISE). An intronic regulatory element that suppresses splicing of an exon is called an intronic splicing suppressor (ISS).

"Instructional material," as that term is used herein, includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the composition and/or compound of the invention in a kit. The instructional material of the kit may, for example, be affixed to a container that contains the compound and/or composition of the invention or be shipped together with a container which contains the compound and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the recipient uses the instructional material and the compound cooperatively. Delivery of the instructional material may be, for example, by physical delivery of the publication or other medium of expression communicating the usefulness of the kit, or may alternatively be achieved by electronic transmission, for example by means of a computer, such as by electronic mail, or download from a website.

By "nucleic acid" is meant any nucleic acid, whether composed of deoxyribonucleosides or ribonucleosides, and whether composed of phosphodiester linkages or modified linkages such as phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, bridged phosphorothioate or sulfone linkages, and combinations of such linkages. The term nucleic acid also specifically includes nucleic acids composed of bases other than the five biologically occurring bases (adenine, guanine, thymine, cytosine and uracil). The term "nucleic acid" typically refers to large polynucleotides.

Conventional notation is used herein to describe polynucleotide sequences: the left-hand end of a single-stranded polynucleotide sequence is the 5'-end; the left-hand direction of a double-stranded polynucleotide sequence is referred to as the 5'-direction.

The direction of 5' to 3' addition of nucleotides to nascent RNA transcripts is referred to as the transcription direction. The DNA strand having the same sequence as an mRNA is referred to as the "coding strand"; sequences on the DNA strand which are located 5' to a reference point on the DNA are referred to as "upstream sequences"; sequences on the DNA strand which are 3' to a reference point on the DNA are referred to as "downstream sequences."

By "expression cassette" is meant a nucleic acid molecule comprising a coding sequence operably linked to promoter/regulatory sequences necessary for transcription and, optionally, translation of the coding sequence.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulator sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a n inducible manner.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced substantially only when an inducer which corresponds to the promoter is present.

"Polypeptide" refers to a polymer composed of amino acid residues, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof linked via peptide bonds. Synthetic polypeptides can be synthesized, for example, using an automated polypeptide synthesizer.

The term "protein" typically refers to large polypeptides.

The term "peptide" typically refers to short polypeptides.

Conventional notation is used herein to portray polypeptide sequences: the left-hand end of a polypeptide sequence is the amino-terminus; the right-hand end of a polypeptide sequence is the carboxyl-terminus.

A "polynucleotide" means a single strand or parallel and anti-parallel strands of a nucleic acid. Thus, a polynucleotide may be either a single-stranded or a double-stranded nucleic acid. In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytidine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

The term "oligonucleotide" typically refers to short polynucleotides, generally no greater than about 60 nucleotides. It will be understood that when a nucleotide sequence is represented by a DNA sequence (i.e., A, T, G, C), this also includes an RNA sequence (i.e., A, U, G, C) in which "U" replaces "T."

The term "recombinant DNA" as used herein is defined as DNA produced by joining pieces of DNA from different sources.

The term "recombinant polypeptide" as used herein is defined as a polypeptide produced by using recombinant DNA methods.

By the term "specifically binds," as used herein, is meant a molecule, such as an antibody, which recognizes and binds to another molecule or feature, but does not substantially recognize or bind other molecules or features in a sample.

By the term "splice defect of a protein", as used herein, is meant a defective protein resulting from a defect in the splicing of an RNA encoding a protein.

The term "treatment," as used herein, refers to reversing, alleviating, delaying the onset of inhibiting the progress of, and/or preventing a disease or disorder, or one or more symptoms thereof, to which the term is applied in a subject. In some embodiments, treatment may be applied after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered prior to symptoms (e.g., in light of a history of symptoms and/or one or more other susceptibility factors), or after symptoms have resolved, for example to prevent or delay their reoccurrence.

Throughout this disclosure, various aspects of this invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual and partial numbers within that range, for example, 1, 2, 3, 4, 5, 5.5 and 6. This applies regardless of the breadth of the range.

Description:

The present invention encompasses a class of compounds known as splice modulating oligonucleotides (SMOs) that modulate pre-mRNA splicing, thereby affecting expression and functionality of a specific protein in a cell. A SMO specifically binds to a complementary sequence on a pre-mRNA at an exon or intron splice suppressor or splice enhancer site, or at an intron-exon splice site. When a SMO specifically binds to a splice enhancer site, or an intron-exon splice site, the adjacent exon is excluded from the resulting mRNA. In another embodiment, a SMO specifically binds to a splice suppressor site or an intron-exon site and the adjacent exon is included in the resulting mRNA. In another embodiment, a SMO specifically binds to a splice enhancer site or an intron-exon splice site and shifts the reading frame of the pre-mRNA so that the resulting protein is a truncated. In some cases, the resulting protein is a limited-function, or non-functional protein.

The location of an exonic or intronic splice enhancer or suppressor motif may be found anywhere within the exon and the flanking introns. Similarly, a SMO may either fully or partially overlap a predicted exonic or intronic splice enhancer or suppressor site in proximity to an intron-exon boundary and/or be complementary to the predicted 3' or 5' splice sites.

I. Compositions: Splice Modulating Oligonucleotides

The present invention is directed, in part, to oligonucleotides referred to herein as splice modulating oligonucleotides (SMOs), suitable for use in modulating splicing of a target pre-mRNA both in vitro and in vivo. The present invention also includes a pharmaceutical composition comprising a SMO suitable for modulating splicing of a target pre-mRNA both in vitro and in vivo. In vivo methodologies are useful for both general splice site modulatory purposes, as well as in therapeutic applications in which modulating splicing of a target pre-mRNA is desirable.

A. 5-Hydroxytryptamine (Serotonin) Receptor 2C (5-HT2CR)

The present invention provides SMOs based on the consensus sequence of the 5-HT2CR(HTR2c; MIM: 312861 GeneID: 3358), including upstream and downstream nucleotides (Table 1). These SMOs are used according to the methods of the invention to modulate splicing of 5-HT2CR pre-mRNA. In one embodiment, these SMOs are used according to the methods of the invention to modulate splicing of 5-HT2CR pre-mRNA caused by a deletion of the 15q11-13 region of the 15th chromosome that results in a deletion of the snoRNA HBII-52. In another embodiment, a SMO of the invention functions to mimic the function of HBII-52. In another embodiment, a SMO of the invention functions to increase expression of a functional 5-HT2CR transcript containing exon 5b.

In some embodiments, the invention includes a pharmaceutical composition that comprises a SMO that functions to modulate splicing of 5-HT2CR pre-mRNA. In other embodiments, the invention includes a pharmaceutical composition that comprises a SMO that functions to modulate splicing of 5-HT2CR pre-mRNA caused by a deletion of the 15q11-13 region of the 15th chromosome that results in a deletion of the snoRNA HBII-52. In another embodiment, the invention includes a pharmaceutical composition that comprises a SMO that functions to mimic the function of HBII-52. In still another embodiment, the invention includes a pharmaceutical composition that comprises a SMO that functions to increase expression of a functional 5-HT2CR transcript containing exon 5b.

Table 1 depicts exemplary SMOs useful for modulating splicing of 5-HT2CR pre-mRNA in order to mimic the effect of HBII-52 snoRNA or increase the expression or function of 5HT2CR containing exon 5b.

TABLE 1

3' to 5' SMOs targeting the 5-HT2C pre-mRNA	SEQ ID NO.
5-HT2C sequence:	
3'-CGAUACGAGUUAUCCUAAUGCAUA-5'	
GCAUUAGGAUAACUCGUA	1
15 nucleotide (nt) SMO	
GGAUAACUCGUAUCG	2
AGGAUAACUCGUAUC	3
UAGGAUAACUCGUAU	4
UUAGGAUAACUCGUA	5
AUUAGGAUAACUCGU	6
CAUUAGGAUAACUCG	7
GCAUUAGGAUAACUC	8
UGCAUUAGGAUAACU	9
AUGCAUUAGGAUAAC	10
UAUGCAUUAGGAUAA	11
16 nt SMO	
AGGAUAACUCGUAUCG	12
UAGGAUAACUCGUAUC	13
UUAGGAUAACUCGUAU	14
AUUAGGAUAACUCGUA	15
CAUUAGGAUAACUCGU	16
GCAUUAGGAUAACUCG	17
UGCAUUAGGAUAACUC	18
AUGCAUUAGGAUAACU	19
UAUGCAUUAGGAUAAC	20
17 nt SMO	
UAGGAUAACUCGUAUCG	21
UUAGGAUAACUCGUAUC	22
AUUAGGAUAACUCGUAU	23
CAUUAGGAUAACUCGUA	24
GCAUUAGGAUAACUCGU	25
UGCAUUAGGAUAACUCG	26
AUGCAUUAGGAUAACUC	27
UAUGCAUUAGGAUAACU	28
18 nt SMO	
GCAUUAGGAUAACUCGUA	29
UUAGGAUAACUCGUAUCG	30
AUUAGGAUAACUCGUAUC	31
CAUUAGGAUAACUCGUAU	32
UGCAUUAGGAUAACUCGU	33
AUGCAUUAGGAUAACUCG	34
UAUGCAUUAGGAUAACUC	35
19 nt SMO	
AUUAGGAUAACUCGUAUCG	36
CAUUAGGAUAACUCGUAUC	37
GCAUUAGGAUAACUCGUAU	38
UGCAUUAGGAUAACUCGUA	39
AUGCAUUAGGAUAACUCGU	40
UAUGCAUUAGGAUAACUCG	41
20 nt SMO	
CAUUAGGAUAACUCGUAUCG	42
GCAUUAGGAUAACUCGUAUC	43
UGCAUUAGGAUAACUCGUAU	44
AUGCAUUAGGAUAACUCGUA	45
UAUGCAUUAGGAUAACUCGU	46
21 nt SMO	
GCAUUAGGAUAACUCGUAUCG	47
UGCAUUAGGAUAACUCGUAUC	48
AUGCAUUAGGAUAACUCGUAU	49
UAUGCAUUAGGAUAACUCGUA	50
22 nt SMO	
UGCAUUAGGAUAACUCGUAUCG	51
AUGCAUUAGGAUAACUCGUAUC	52
UAUGCAUUAGGAUAACUCGUAU	53
23 nt SMO	
AUGCAUUAGGAUAACUCGUAUCG	54
UAUGCAUUAGGAUAACUCGUAUC	55
24 nt SMO	
UAUGCAUUAGGAUAACUCGUAUCG	56

B. Glutamate Receptors

The present invention further provides SMOs based on the sequences of the flip and flop isoforms of GluR1 (GRIA1; MIM: 138248 GeneID: 2890), GluR2 (GRIA2; MIM: 138247 GeneID: 2891), GluR3 (GRIA3; MIM: 305915 GeneID: 2892), and GluR4 (GRIA4; MIM: 138246 GeneID: 2893). These SMOs are used according to the methods of the invention to modulate splicing of GluR pre-mRNA. In one embodiment, a SMO of the invention functions to decrease GluR flip isoform expression. In another embodiment, a SMO of the invention functions to decrease the GluR flip/flop isoform ratio. In yet another embodiment, a SMO of the invention functions to increase the GluR flop isoform. In still another embodiment, a SMO of the invention functions to increase the GluR flop isoforms. In various embodiments, a SMO of the invention functions to decrease both the GluR flip and GluR flop isoform expression.

In various embodiments, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease the GluR flip isoform expression. In other embodiments, the invention includes a pharmaceutical composition comprising a SMO that decrease the GluR flip/flop isoform ratio of expression. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO that functions to increase the GluR flop isoform expression. In yet another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention that functions to decrease both the GluR flip and GluR flop isoform expression.

Table 2 depicts exemplary SMOs useful for modulating splicing of GluR3 pre-mRNA in order to decrease GluR3-flip expression or increase GluR3-flop expression in a cell.

TABLE 2

3' to 5' Splice modulating oligonucleotides directed to GluR3-flip pre-mRNA	SEQ ID NO.
aaagggugcacuucUUGCGGACAU	57
aagggugcacuucUUGCGGACAUU	58
agggugcacuucUUGCGGACAUUU	59
gggugcacuucUUGCGGACAUUUG	60
ggugcacuucUUGCGGACAUUUGG	61
gugcacuucUUGCGGACAUUUGGA	62
ugcacuucUUGCGGACAUUUGGAA	63
gcacuucUUGCGGACAUUUGGAAC	64
cacuucUUGCGGACAUUUGGAACG	65
acuucUUGCGGACAUUUGGAACGU	66
cuucUUGCGGACAUUUGGAACGUC	67
uucUUGCGGACAUUUGGAACGUCA	68
ucUUGCGGACAUUUGGAACGUCAU	69
cUUGCGGACAUUUGGAACGUCAUA	70
UUGCGGACAUUUGGAACGUCAUAA	71
UGCGGACAUUUGGAACGUCAUAAC	72
GCGGACAUUUGGAACGUCAUAACU	73
aaagggugcacuucUUGCGGACA	74
aagggugcacuucUUGCGGACAU	75
agggugcacuucUUGCGGACAUU	76
gggugcacuucUUGCGGACAUUU	77
ggugcacuucUUGCGGACAUUUG	78
gugcacuucUUGCGGACAUUUGG	79
ugcacuucUUGCGGACAUUUGGA	80
gcacuucUUGCGGACAUUUGGAA	81
cacuucUUGCGGACAUUUGGAAC	82
acuucUUGCGGACAUUUGGAACG	83
cuucUUGCGGACAUUUGGAACGU	84
uucUUGCGGACAUUUGGAACGUC	85
ucUUGCGGACAUUUGGAACGUCA	86
cUUGCGGACAUUUGGAACGUCAU	87
UUGCGGACAUUUGGAACGUCAUA	88
UGCGGACAUUUGGAACGUCAUAA	89
GCGGACAUUUGGAACGUCAUAAC	90
CGGACAUUUGGAACGUCAUAACU	91
aaagggugcacuucUUGCGGAC	92
aagggugcacuucUUGCGGACA	93
agggugcacuucUUGCGGACAU	94
gggugcacuucUUGCGGACAUU	95
ggugcacuucUUGCGGACAUUU	96
gugcacuucUUGCGGACAUUUG	97
ugcacuucUUGCGGACAUUUGG	98
gcacuucUUGCGGACAUUUGGA	99
cacuucUUGCGGACAUUUGGAA	100
acuucUUGCGGACAUUUGGAAC	101
cuucUUGCGGACAUUUGGAACG	102
uucUUGCGGACAUUUGGAACGU	103
ucUUGCGGACAUUUGGAACGUC	104
cUUGCGGACAUUUGGAACGUCA	105
UUGCGGACAUUUGGAACGUCAU	106
UGCGGACAUUUGGAACGUCAUA	107
GCGGACAUUUGGAACGUCAUAA	108
CGGACAUUUGGAACGUCAUAAC	109
GGACAUUUGGAACGUCAUAACU	110
aaagggugcacuucUUGCGGA	111
aagggugcacuucUUGCGGAC	112
agggugcacuucUUGCGGACA	113
gggugcacuucUUGCGGACAU	114
ggugcacuucUUGCGGACAUU	115
gugcacuucUUGCGGACAUUU	116

TABLE 2-continued

3' to 5' Splice modulating oligonucleotides directed to GluR3-flip pre-mRNA	SEQ ID NO.
ugcacuucUUGCGGACAUUUG	117
gcacuucUUGCGGACAUUUGG	118
cacuucUUGCGGACAUUUGGA	119
acuucUUGCGGACAUUUGGAA	120
cuucUUGCGGACAUUUGGAAC	121
uucUUGCGGACAUUUGGAACG	122
ucUUGCGGACAUUUGGAACGU	123
cUUGCGGACAUUUGGAACGUC	124
UUGCGGACAUUUGGAACGUCA	125
UGCGGACAUUUGGAACGUCAU	126
GCGGACAUUUGGAACGUCAUA	127
CGGACAUUUGGAACGUCAUAA	128
GGACAUUUGGAACGUCAUAAC	129
GACAUUUGGAACGUCAUAACU	130
aaagggugcacuucUUGCGG	131
aagggugcacuucUUGCGGA	132
agggugcacuucUUGCGGAC	133
gggugcacuucUUGCGGACA	134
ggugcacuucUUGCGGACAU	135
gugcacuucUUGCGGACAUU	136
ugcacuucUUGCGGACAUUU	137
gcacuucUUGCGGACAUUUG	138
cacuucUUGCGGACAUUUGG	139
acuucUUGCGGACAUUUGGA	140
cuucUUGCGGACAUUUGGAA	141
uucUUGCGGACAUUUGGAAC	142
ucUUGCGGACAUUUGGAACG	143
cUUGCGGACAUUUGGAACGU	144
UUGCGGACAUUUGGAACGUC	145
UGCGGACAUUUGGAACGUCA	146
GCGGACAUUUGGAACGUCAU	147
CGGACAUUUGGAACGUCAUA	148
GGACAUUUGGAACGUCAUAA	149
aaagggugcacuucUUGCG	150
aagggugcacuucUUGCGG	151
agggugcacuucUUGCGGA	152
gggugcacuucUUGCGGAC	153
ggugcacuucUUGCGGACA	154
gugcacuucUUGCGGACAU	155
ugcacuucUUGCGGACAUU	156
gcacuucUUGCGGACAUUU	157
cacuucUUGCGGACAUUUG	158
acuucUUGCGGACAUUUGG	159
cuucUUGCGGACAUUUGGA	160
uucUUGCGGACAUUUGGAA	161
ucUUGCGGACAUUUGGAAC	162
cUUGCGGACAUUUGGAACG	163
UUGCGGACAUUUGGAACGU	164
UGCGGACAUUUGGAACGUC	165
GCGGACAUUUGGAACGUCA	166
CGGACAUUUGGAACGUCAU	167
GGACAUUUGGAACGUCAUA	168
aaagggugcacuucUUGC	169
aagggugcacuucUUGCG	170
agggugcacuucUUGCGG	171
gggugcacuucUUGCGGA	172
ggugcacuucUUGCGGAC	173
gugcacuucUUGCGGACA	174
ugcacuucUUGCGGACAU	175
gcacuucUUGCGGACAUU	176
cacuucUUGCGGACAUUU	177
acuucUUGCGGACAUUUG	178
cuucUUGCGGACAUUUGG	179
uucUUGCGGACAUUUGGA	180
ucUUGCGGACAUUUGGAA	181
cUUGCGGACAUUUGGAAC	182
UUGCGGACAUUUGGAACG	183
UGCGGACAUUUGGAACGU	184
GCGGACAUUUGGAACGUC	185
CGGACAUUUGGAACGUCA	186
GGACAUUUGGAACGUCAU	187

Table 3 depicts exemplary SMOs for modulating splicing of GluR1 pre-mRNA in order to decrease GluR1-flip expression or increase GluR1-flop expression in a cell.

TABLE 3

3' to 5' Splice modulating oligonucleotides directed to GluR1-flip pre-mRNA	SEQ ID NO.
caacuucUCCAGGGCAUUUGGAUC	188
aacuucUCCAGGGCAUUUGGAUCG	189
acuucUCCAGGGCAUUUGGAUCGC	190
cuucUCCAGGGCAUUUGGAUCGCC	191
uucUCCAGGGCAUUUGGAUCGCCA	192
ucUCCAGGGCAUUUGGAUCGCCAA	193
cUCCAGGGCAUUUGGAUCGCCAAA	194
UCCAGGGCAUUUGGAUCGCCAAAA	195
caacuucUCCAGGGCAUUUGGAU	196
aacuucUCCAGGGCAUUUGGAUC	197
acuucUCCAGGGCAUUUGGAUCG	198
cuucUCCAGGGCAUUUGGAUCGC	199
uucUCCAGGGCAUUUGGAUCGCC	200
ucUCCAGGGCAUUUGGAUCGCCA	201
cUCCAGGGCAUUUGGAUCGCCAA	202
UCCAGGGCAUUUGGAUCGCCAAA	203
CCAGGGCAUUUGGAUCGCCAAAA	204
caacuucUCCAGGGCAUUUGGA	205
aacuucUCCAGGGCAUUUGGAU	206
acuucUCCAGGGCAUUUGGAUC	207
cuucUCCAGGGCAUUUGGAUCG	208
uucUCCAGGGCAUUUGGAUCGC	209
ucUCCAGGGCAUUUGGAUCGCC	210
cUCCAGGGCAUUUGGAUCGCCA	211
UCCAGGGCAUUUGGAUCGCCAA	212
CCAGGGCAUUUGGAUCGCCAAA	213
caacuucUCCAGGGCAUUUGG	214
aacuucUCCAGGGCAUUUGGA	215
acuucUCCAGGGCAUUUGGAU	216
cuucUCCAGGGCAUUUGGAUC	217
uucUCCAGGGCAUUUGGAUCG	218
ucUCCAGGGCAUUUGGAUCGC	219
cUCCAGGGCAUUUGGAUCGCC	220
UCCAGGGCAUUUGGAUCGCCA	221
CCAGGGCAUUUGGAUCGCCAA	222
caacuucUCCAGGGCAUUUG	223
aacuucUCCAGGGCAUUUGG	224
acuucUCCAGGGCAUUUGGA	225
cuucUCCAGGGCAUUUGGAU	226
uucUCCAGGGCAUUUGGAUC	227
ucUCCAGGGCAUUUGGAUCG	228
cUCCAGGGCAUUUGGAUCGC	229
UCCAGGGCAUUUGGAUCGCC	230
CCAGGGCAUUUGGAUCGCCA	231
caacuucUCCAGGGCAUUU	232
aacuucUCCAGGGCAUUUG	233
acuucUCCAGGGCAUUUGG	234
cuucUCCAGGGCAUUUGGA	235
uucUCCAGGGCAUWGGAU	236
ucUCCAGGGCAUUUGGAUC	237
cUCCAGGGCAUUUGGAUCG	238
UCCAGGGCAUUUGGAUCGC	239
CCAGGGCAUUUGGAUCGCC	240
caacuucUCCAGGGCAUU	241
aacuucUCCAGGGCAUUU	242
acuucUCCAGGGCAUUUG	243
cuucUCCAGGGCAUUUGG	244
uucUCCAGGGCAUUUGGA	245
ucUCCAGGGCAUUUGGAU	246
cUCCAGGGCAUUUGGAUC	247
UCCAGGGCAUUUGGAUCG	248
CCAGGGCAUUUGGAUCGC	249
ACCUUCGUUCCUGAGGCCUUCAUU	250
CCUUCGUUCCUGAGGCCUUCAUUC	251
CUUCGUUCCUGAGGCCUUCAUUCc	252
UUCGUUCCUGAGGCCUUCAUUCca	253
UCGUUCCUGAGGCCUUCAUUCcag	254
CGUUCCUGAGGCCUUCAUUCcagu	255
GUUCCUGAGGCCUUCAUUCcaguc	256
UUCCUGAGGCCUUCAUUCcaguca	257
CCUUCGUUCCUGAGGCCUUCAUU	258
CUUCGUUCCUGAGGCCUUCAUUC	259
UUCGUUCCUGAGGCCUUCAUUCc	260
UCGUUCCUGAGGCCUUCAUUCca	261
CGUUCCUGAGGCCUUCAUUCcag	262
GUUCCUGAGGCCUUCAUUCcagu	263

TABLE 3-continued

3' to 5' Splice modulating oligonucleotides directed to GluR1-flip pre-mRNA	SEQ ID NO.
UUCCUGAGGCCUUCAUUCcaguc	264
UCCUGAGGCCUUCAUUCcaguca	265
CUUCGUUCCUGAGGCCUUCAUU	266
UUCGUUCCUGAGGCCUUCAUUC	267
UCGUUCCUGAGGCCUUCAUUCc	268
CGUUCCUGAGGCCUUCAUUCca	269
GUUCCUGAGGCCUUCAUUCcag	270
UUCCUGAGGCCUUCAUUCcagu	271
UCCUGAGGCCUUCAUUCcaguc	272
CCUGAGGCCUUCAUUCcaguca	273
UUCGUUCCUGAGGCCUUCAUU	274
UCGUUCCUGAGGCCUUCAUUC	275
CGUUCCUGAGGCCUUCAUUCc	276
GUUCCUGAGGCCUUCAUUCca	277
UUCCUGAGGCCUUCAUUCcag	278
UCCUGAGGCCUUCAUUCcagu	279
CCUGAGGCCUUCAUUCcaguc	280
CUGAGGCCUUCAUUCcaguca	281
UCGUUCCUGAGGCCUUCAUU	282
CGUUCCUGAGGCCUUCAUUC	283
GUUCCUGAGGCCUUCAUUCc	284
UUCCUGAGGCCUUCAUUCca	285
UCCUGAGGCCUUCAUUCcag	286
CCUGAGGCCUUCAUUCcagu	287
CUGAGGCCUUCAUUCcaguc	288
UGAGGCCUUCAUUCcaguca	289
CGUUCCUGAGGCCUUCAUU	290
GUUCCUGAGGCCUUCAUUC	291
UUCCUGAGGCCUUCAUUCc	292
UCCUGAGGCCUUCAUUCca	293
CCUGAGGCCUUCAUUCcag	294
CUGAGGCCUUCAUUCcagu	295
UGAGGCCUUCAUUCcaguc	296
GAGGCCUUCAUUCcaguca	297
GUUCCUGAGGCCUUCAUU	298
UUCCUGAGGCCUUCAUUC	299
UCCUGAGGCCUUCAUUCc	300
CCUGAGGCCUUCAUUCca	301
CUGAGGCCUUCAUUCcag	302
UGAGGCCUUCAUUCcagu	303
GAGGCCUUCAUUCcaguc	304
AGGCCUUCAUUCcaguca	305

Table 4 depicts exemplary SMOs for modulating splicing of all GluR subtypes, including GluR1, GluR2, GluR3, and GluR4 pre-mRNA in order to decrease GluR1-4-flip expression or increase GluR1-4-flop expression in a cell.

TABLE 4

3' to 5' SMOs targeting GluR1, GluR2, GluR3, and GluR4	SEQ ID NO.
UUCCGCAGAUUCUGUUCGACUUUU	306
UUCCGCAGAUUCUGUUCGACUUU	307
UCCGCAGAUUCUGUUCGACUUUU	308
UUCCGCAGAUUCUGUUCGACUU	309
UCCGCAGAUUCUGUUCGACUUU	310
CCGCAGAUUCUGUUCGACUUUU	311
UUCCGCAGAUUCUGUUCGACU	312
UCCGCAGAUUCUGUUCGACUU	313
CCGCAGAUUCUGUUCGACUUU	314
CGCAGAUUCUGUUCGACUUUU	315
UUCCGCAGAUUCUGUUCGAC	316
UCCGCAGAUUCUGUUCGACU	317
CCGCAGAUUCUGUUCGACUU	318
CGCAGAUUCUGUUCGACUUU	319
GCAGAUUCUGUUCGACUUUU	320
UUCCGCAGAUUCUGUUCGA	321
UCCGCAGAUUCUGUUCGAC	322
CCGCAGAUUCUGUUCGACU	323
CGCAGAUUCUGUUCGACUU	324
GCAGAUUCUGUUCGACUUU	325
CAGAUUCUGUUCGACUUUU	326
UUCCGCAGAUUCUGUUCG	327
UCCGCAGAUUCUGUUCGA	328
CCGCAGAUUCUGUUCGAC	329
CGCAGAUUCUGUUCGACU	330
GCAGAUUCUGUUCGACUU	331
CAGAUUCUGUUCGACUUU	332

TABLE 4-continued

3' to 5' SMOs targeting GluR1, GluR2, GluR3, and GluR4	SEQ ID NO.
AGAUUCUGUUCGACUUUU	333
UUGUUCCGUAGAAUCUGUUCGACU	334
UGUUCCGUAGAAUCUGUUCGACUU	335
GUUCCGUAGAAUCUGUUCGACUUU	336
UUCCGUAGAAUCUGUUCGACUUUU	337
UUGUUCCGUAGAAUCUGUUCGAC	338
UGUUCCGUAGAAUCUGUUCGACU	339
GUUCCGUAGAAUCUGUUCGACUU	340
UUCCGUAGAAUCUGUUCGACUUU	341
UCCGUAGAAUCUGUUCGACUUUU	342
UUGUUCCGUAGAAUCUGUUCGA	343
UGUUCCGUAGAAUCUGUUCGAC	344
GUUCCGUAGAAUCUGUUCGACU	345
UUCCGUAGAAUCUGUUCGACUU	346
UCCGUAGAAUCUGUUCGACUUU	347
CCGUAGAAUCUGUUCGACUUUU	348
UUGUUCCGUAGAAUCUGUUCG	349
UGUUCCGUAGAAUCUGUUCGA	350
GUUCCGUAGAAUCUGUUCGAC	351
UUCCGUAGAAUCUGUUCGACU	352
UCCGUAGAAUCUGUUCGACUU	353
CCGUAGAAUCUGUUCGACUUU	354
CGUAGAAUCUGUUCGACUUUU	355
UUGUUCCGUAGAAUCUGUUC	356
UGUUCCGUAGAAUCUGUUCG	357
GUUCCGUAGAAUCUGUUCGA	358
UUCCGUAGAAUCUGUUCGAC	359
UCCGUAGAAUCUGUUCGACU	360
CCGUAGAAUCUGUUCGACUU	361
UUCCGUAGAAUCUGUUCGA	362
UCCGUAGAAUCUGUUCGAC	363
CCGUAGAAUCUGUUCGACU	364
CGUAGAAUCUGUUCGACUU	365
UUCCGUAGAAUCUGUUCG	366
UCCGUAGAAUCUGUUCGA	367
CCGUAGAAUCUGUUCGAC	368
CGUAGAAUCUGUUCGACU	369
ACUUUUCGUUUACCACCAUGCU	370
ACUUUUCGUUUACCACCAUGC	371
CUUUUCGUUUACCACCAUGCU	372
CUUUUCGUUUACCACCAUGC	373
CUUUUCGUUUACCACCAUGC	374
UUUUCGUUUACCACCAUGCU	375
UUUGAGUCACUUGUUCCGUAGAAU	376
UUUGAGUCACUUGUUCCGUAGAA	377
UUGAGUCACUUGUUCCGUAGAAU	378
UUUGAGUCACUUGUUCCGUAGA	379
UUGAGUCACUUGUUCCGUAGAA	380
UGAGUCACUUGUUCCGUAGAAU	381
UUUGAGUCACUUGUUCCGUAG	382
UUGAGUCACUUGUUCCGUAGA	383
UGAGUCACUUGUUCCGUAGAA	384
GAGUCACUUGUUCCGUAGAAU	385
UUUGAGUCACUUGUUCCGUA	386
UUGAGUCACUUGUUCCGUAG	387
UGAGUCACUUGUUCCGUAGA	388
GAGUCACUUGUUCCGUAGAA	389
AGUCACUUGUUCCGUAGAAU	390
UUUGAGUCACUUGUUCCGU	391
UUGAGUCACUUGUUCCGUA	392
UGAGUCACUUGUUCCGUAG	393
GAGUCACUUGUUCCGUAGA	394
AGUCACUUGUUCCGUAGAA	395
GUCACUUGUUCCGUAGAAU	396
UUGAGUCACUUGUUCCGU	397
UGAGUCACUUGUUCCGUA	398
GAGUCACUUGUUCCGUAG	399
AGUCACUUGUUCCGUAGA	400

Table 5 depicts exemplary SMOs for modulating splicing of GluR2 pre-mRNA in order to decrease GluR2-flip expression or increase GluR2-flop expression in a cell.

TABLE 5

3' to 5' Splice modulating oligonucleotidesdirected to flip GluR2	SEQ ID NO.
gcacuucUUGGGGUCAUUUAGAAC	401
cacuucUUGGGGUCAUUUAGAACG	402

TABLE 5-continued

3' to 5' Splice modulating oligonucleotidesdirected to flip GluR2	SEQ ID NO.
acuucUUGGGGUCAUUUAGAACGU	403
cuucUUGGGGUCAUUUAGAACGUC	404
uucUUGGGGUCAUUUAGAACGUCA	405
ucUUGGGGUCAUUUAGAACGUCAU	406
cUUGGGGUCAUUUAGAACGUCAUA	407
UUGGGGUCAUUUAGAACGUCAUAA	408
UGGGGUCAUUUAGAACGUCAUAAC	409
gcacuucUUGGGGUCAUUUAGAA	410
cacuucUUGGGGUCAUUUAGAAC	411
acuucUUGGGGUCAUUUAGAACG	412
cuucUUGGGGUCAUUUAGAACGU	413
uucUUGGGGUCAUUUAGAACGUC	414
ucUUGGGGUCAUUUAGAACGUCA	415
cUUGGGGUCAUUUAGAACGUCAU	416
UUGGGGUCAUUUAGAACGUCAUA	417
UGGGGUCAUUUAGAACGUCAUAA	418
gcacuucUUGGGGUCAUUUAGA	419
cacuucUUGGGGUCAUUUAGAA	420
acuucUUGGGGUCAUUUAGAAC	421
cuucUUGGGGUCAUUUAGAACG	422
uucUUGGGGUCAUUUAGAACGU	423
ucUUGGGGUCAUUUAGAACGUC	424
cUUGGGGUCAUUUAGAACGUCA	425
UUGGGGUCAUUUAGAACGUCAU	426
UGGGGUCAUUUAGAACGUCAUA	427
gcacuucUUGGGGUCAUUUAG	428
cacuucUUGGGGUCAUUUAGA	429
acuucUUGGGGUCAUUUAGAA	430
cuucUUGGGGUCAUUUAGAAC	431
uucUUGGGGUCAUUUAGAACG	432
ucUUGGGGUCAUUUAGAACGU	433
cUUGGGGUCAUUUAGAACGUC	434
UUGGGGUCAUUUAGAACGUCA	435
UGGGGUCAUUUAGAACGUCAU	436
gcacuucUUGGGGUCAUUUA	437
cacuucUUGGGGUCAUUUAG	438
acuucUUGGGGUCAUUUAGA	439
cuucUUGGGGUCAUUUAGAA	440
uucUUGGGGUCAUUUAGAAC	441
ucUUGGGGUCAUUUAGAACG	442
cUUGGGGUCAUUUAGAACGU	443
UUGGGGUCAUUUAGAACGUC	444
UGGGGUCAUUUAGAACGUCA	445
gcacuucUUGGGGUCAUUU	446
cacuucUUGGGGUCAUUUA	447
acuucUUGGGGUCAUUUAG	448
cuucUUGGGGUCAUUUAGA	449
uucUUGGGGUCAUUUAGAA	450
ucUUGGGGUCAUUUAGAAC	451
cUUGGGGUCAUUUAGAACG	452
UUGGGGUCAUUUAGAACGU	453
UGGGGUCAUUUAGAACGUC	454
gcacuucUUGGGGUCAUU	455
cacuucUUGGGGUCAUUU	456
acuucUUGGGGUCAUUUA	457
cuucUUGGGGUCAUUUAG	458
uucUUGGGGUCAUUUAGA	459
ucUUGGGGUCAUUUAGAA	460
cUUGGGGUCAUUUAGAAC	461
UUGGGGUCAUUUAGAACG	462
UGGGGUCAUUUAGAACGU	463

Table 6 depicts exemplary SMOs for modulating splicing of GluR4 pre-mRNA in order to decrease GluR4-flip expression or increase GluR4-flop expression in a cell.

TABLE 6

3' to 5' Splice modulating oligonucleotides directed to all flip GluR4	SEQ ID NO.
gcacuucUUGAGGACAUUUGGAAC	464
cacuucUUGAGGUCAUUUGGAACG	465
acuucUUGAGGUCAUUUGGAACGG	466
cuucUUGAGGUCAUUUGGAACGGC	467
uucUUGAGGUCAUUUGGAACGGCA	468
ucUUGAGGUCAUUUGGAACGGCAA	469
cUUGAGGUCAUUUGGAACGGCAAA	470
UUGAGGUCAUUUGGAACGGCAAAA	471
UGAGGUCAUUUGGAACGGCAAAAC	472

TABLE 6-continued

3' to 5' Splice modulating oligonucleotides directed to all flip GluR4	SEQ ID NO.
gcacuucUUGAGGACAUUUGGAA	473
cacuucUUGAGGUCAUUUGGAAC	474
acuucUUGAGGUCAUUUGGAACG	475
cuucUUGAGGUCAUUUGGAACGG	476
uucUUGAGGUCAUUUGGAACGGC	477
ucUUGAGGUCAUUUGGAACGGCA	478
cUUGAGGUCAUUUGGAACGGCAA	479
UUGAGGUCAUUUGGAACGGCAAA	480
UGAGGUCAUUUGGAACGGCAAAA	481
gcacuucUUGAGGACAUUUGGA	482
cacuucUUGAGGUCAUUUGGAA	483
acuucUUGAGGUCAUUUGGAAC	484
cuucUUGAGGUCAUUUGGAACG	485
uucUUGAGGUCAUUUGGAACGG	486
ucUUGAGGUCAUUUGGAACGGC	487
cUUGAGGUCAUUUGGAACGGCA	488
UUGAGGUCAUUUGGAACGGCAA	489
UGAGGUCAUUUGGAACGGCAAA	490
gcacuucUUGAGGACAUUUGG	491
cacuucUUGAGGUCAUUUGGA	492
acuucUUGAGGUCAUUUGGAA	493
cuucUUGAGGUCAUUUGGAAC	494
uucUUGAGGUCAUUUGGAACG	495
ucUUGAGGUCAUUUGGAACGG	496
cUUGAGGUCAUUUGGAACGGC	497
UUGAGGUCAUUUGGAACGGCA	498
UGAGGUCAUUUGGAACGGCAA	499
gcacuucUUGAGGACAUUUG	500
cacuucUUGAGGUCAUUUGG	501
acuucUUGAGGUCAUUUGGA	502
cuucUUGAGGUCAUUUGGAA	503
uucUUGAGGUCAUUUGGAAC	504
ucUUGAGGUCAUUUGGAACG	505
cUUGAGGUCAUUUGGAACGG	506
UUGAGGUCAUUUGGAACGGC	507
UGAGGUCAUUUGGAACGGCA	508
gcacuucUUGAGGACAUUU	509
cacuucUUGAGGUCAUUUG	510
acuucUUGAGGUCAUUUGG	511
cuucUUGAGGUCAUUUGGA	512
uucUUGAGGUCAUUUGGAA	513
ucUUGAGGUCAUUUGGAAC	514
cUUGAGGUCAUUUGGAACG	515
UUGAGGUCAUUUGGAACGG	516
UGAGGUCAUUUGGAACGGC	517
gcacuucUUGAGGACAUU	518
cacuucUUGAGGUCAUUU	519
acuucUUGAGGUCAUUUG	520
cuucUUGAGGUCAUUUGG	521
uucUUGAGGUCAUUUGGA	522
ucUUGAGGUCAUUUGGAA	523
cUUGAGGUCAUUUGGAAC	524
UUGAGGUCAUUUGGAACG	525
UGAGGUCAUUUGGAACGG	526

C. O-GlcNAcase (OGA)

The present invention further provides SMOs based on the sequences of OGA (MGEA5; MIM: 604039; GeneID: 10724). These SMOs are used according to the methods of the invention to modulate splicing of OGA pre-mRNA. In one embodiment, a SMO of the invention functions to decrease OGA expression or function. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease the OGA expression or function. In one aspect, an alternative splice variant of OGA with reduced catalytic activity comprises OGA 10t, a read-through variant which results in 15 amino acids being added from intron 10. In another aspect, an alternative splice variant of OGA with reduced catalytic activity comprises OGAΔ8 wherein exon 8 of the OGA gene is excluded.

Table 7 depicts exemplary SMOs for modulating splicing of exon 8 of OGA pre-mRNA in order to produce an OGA protein with lower enzymatic activity in a cell.

TABLE 7

3' to 5' Splice modulating oligonucleotides targeting Exon 8 of OGA	SEQ ID NO.
gucGACUGUCACUUCUGUCAUGAC	527
ucGACUGUCACUUCUGUCAUGACA	528
cGACUGUCACUUCUGUCAUGACAU	529
UCUUUUACUUCCGUCACUGCUUCU	530
CACUGCUUCUGUAACUUUGACUAC	531

TABLE 7-continued

3' to 5' Splice modulating oligonucleotides targeting Exon 8 of OGA	SEQ ID NO.
ACUGCUUCUGUAACUUUGACUACA	532
gucGACUGUCACUUCUGUCAUGA	533
ucGACUGUCACUUCUGUCAUGAC	534
cGACUGUCACUUCUGUCAUGACA	535
UCUUUUACUUCCGUCACUGCUUC	536
CUUUUACUUCCGUCACUGCUUCU	537
CACUGCUUCUGUAACUUUGACUA	538
ACUGCUUCUGUAACUUUGACUAC	539
CUGCUUCUGUAACUUUGACUACA	540
GGAGUAGUUAUGUCGUcacucaa	541
gucGACUGUCACUUCUGUCAUG	542
ucGACUGUCACUUCUGUCAUGA	543
cGACUGUCACUUCUGUCAUGAC	544
UCUUUUACUUCCGUCACUGCUU	545
CUUUUACUUCCGUCACUGCUUC	546
UUUUACUUCCGUCACUGCUUCU	547
CACUGCUUCUGUAACUUUGACU	548
ACUGCUUCUGUAACUUUGACUA	549
CUGCUUCUGUAACUUUGACUAC	550
UGCUUCUGUAACUUUGACUACA	551
GGAGUAGUUAUGUCGUcacuca	552
GAGUAGUUAUGUCGUcacucaa	553
gucGACUGUCACUUCUGUCAU	554
ucGACUGUCACUUCUGUCAUG	555
cGACUGUCACUUCUGUCAUGA	556
UCUUUUACUUCCGUCACUGCU	557
CUUUUACUUCCGUCACUGCUU	558
UUUUACUUCCGUCACUGCUUC	559
UUUACUUCCGUCACUGCUUCU	560
CACUGCUUCUGUAACUUUGAC	561
ACUGCUUCUGUAACUUUGACU	562
CUGCUUCUGUAACUUUGACUA	563
UGCUUCUGUAACUUUGACUAC	564
GCUUCUGUAACUUUGACUACA	565
GGAGUAGUUAUGUCGUcacuc	566
GAGUAGUUAUGUCGUcacuca	567
AGUAGUUAUGUCGUcacucaa	568
gucGACUGUCACUUCUGUCA	569
ucGACUGUCACUUCUGUCAU	570
cGACUGUCACUUCUGUCAUG	571
UCUUUUACUUCCGUCACUGC	572
CUUUUACUUCCGUCACUGCU	573
UUUUACUUCCGUCACUGCUU	574
UUUACUUCCGUCACUGCUUC	575
UUACUUCCGUCACUGCUUCU	576
CACUGCUUCUGUAACUUUGA	577
ACUGCUUCUGUAACUUUGAC	578
CUGCUUCUGUAACUUUGACU	579
UGCUUCUGUAACUUUGACUA	580
GCUUCUGUAACUUUGACUAC	581
CUUCUGUAACUUUGACUACA	582
GGAGUAGUUAUGUCGUcacu	583
GAGUAGUUAUGUCGUcacuc	584
AGUAGUUAUGUCGUcacuca	585
GUAGUUAUGUCGUcacucaa	586
gucGACUGUCACUUCUGUC	587
ucGACUGUCACUUCUGUCA	588
cGACUGUCACUUCUGUCAU	589
UCUUUUACUUCCGUCACUG	590
CUUUUACUUCCGUCACUGC	591
UUUUACUUCCGUCACUGCU	592
UUUACUUCCGUCACUGCUU	593
UUACUUCCGUCACUGCUUC	594
UACUUCCGUCACUGCUUCU	595
GGAGUAGUUAUGUCGUcac	596
GAGUAGUUAUGUCGUcacu	597
AGUAGUUAUGUCGUcacuc	598
GUAGUUAUGUCGUcacuca	599
UAGUUAUGUCGUcacucaa	600
agugucGACUGUCACUUC	601
gucGACUGUCACUUCUGU	602
ucGACUGUCACUUCUGUC	603
cGACUGUCACUUCUGUCA	604
ACUUCCGUCACUGCUUCU	605
GGAGUAGUUAUGUCGUca	606
GAGUAGUUAUGUCGUcac	607

TABLE 7-continued

3' to 5' Splice modulating oligonucleotides targeting Exon 8 of OGA	SEQ ID NO.
AGUAGUUAUGUCGUcacu	608
GUAGUUAUGUCGUcacuc	609
UAGUUAUGUCGUcacuca	610
AGUUAUGUCGUcacucaa	611

Table 8 depicts exemplary SMOs for modulating splicing of exon 10 of OGA pre-mRNA in order to produce an OGA protein with lower enzymatic activity in a cell.

TABLE 8

3' to 5' Splice modulating oligonucleotides directed exon 10 of OGA	SEQ ID NO.
UUUAGAAAACAUGUCACCAAUCca	612
UUAGAAAACAUGUCACCAAUCcau	613
UAGAAAACAUGUCACCAAUCcauc	614
AGAAAACAUGUCACCAAUCcaucc	615
GAAAACAUGUCACCAAUCcaucca	616
UUAGAAAACAUGUCACCAAUCca	617
UAGAAAACAUGUCACCAAUCcau	618
AGAAAACAUGUCACCAAUCcauc	619
GAAAACAUGUCACCAAUCcaucc	620
AAAACAUGUCACCAAUCcaucca	621
UAGAAAACAUGUCACCAAUCca	622
AGAAAACAUGUCACCAAUCcau	623
GAAAACAUGUCACCAAUCcauc	624
AAAACAUGUCACCAAUCcaucc	625
AAACAUGUCACCAAUCcaucca	626
GAUACCACUUUAGAAAACAUGU	627
AGAAAACAUGUCACCAAUCca	628
GAAAACAUGUCACCAAUCcau	629
AAAACAUGUCACCAAUCcauc	630
AAACAUGUCACCAAUCcaucc	631
AACAUGUCACCAAUCcaucca	632
GAUACCACUUUAGAAAACAUG	633
AUACCACUUUAGAAAACAUGU	634
GAAAACAUGUCACCAAUCca	635
AAAACAUGUCACCAAUCcau	636
AAACAUGUCACCAAUCcauc	637
AACAUGUCACCAAUCcaucc	638
ACAUGUCACCAAUCcaucca	639
GAUACCACUUUAGAAAACAU	640
AUACCACUUUAGAAAACAUG	641
UACCACUUUAGAAAACAUGU	642
AAAACAUGUCACCAAUCca	643
AAACAUGUCACCAAUCcau	644
AACAUGUCACCAAUCcauc	645
ACAUGUCACCAAUCcaucc	646
CAUGUCACCAAUCcaucca	647
GAUACCACUUUAGAAAACA	648
AUACCACUUUAGAAAACAU	649
UACCACUUUAGAAAACAUG	650
ACCACUUUAGAAAACAUGU	651
AAACAUGUCACCAAUCca	652
AACAUGUCACCAAUCcau	653
ACAUGUCACCAAUCcauc	654
CAUGUCACCAAUCcaucc	655
AUGUCACCAAUCcaucca	656
GAUACCACUUUAGAAAAC	657
AUACCACUUUAGAAAACA	658
UACCACUUUAGAAAACAU	659
ACCACUUUAGAAAACAUG	660
CCACUUUAGAAAACAUGU	661

D. Aph1B

The present invention further provides SMOs based on the sequences of Aph1B (APH1B; MIM: 607630; GeneID: 83464). These SMOs are used according to the methods of the invention to modulate splicing of Aph1B pre-mRNA. In one embodiment, a SMO of the invention functions to decrease Aph1B expression or function. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease the Aph1B expression or function. In one aspect, the SMO contacts an Aph1B pre-mRNA and modulates the splicing of the Aph1B pre-mRNA such that “in-frame” exon 4 is skipped, resulting in Aph1BΔ4, a non-functional protein.

Table 9 depicts exemplary SMOs for modulating splicing of Alph1B pre-mRNA in order to produce a non-functional protein with lower enzymatic activity in a cell.

TABLE 9

3' to 5' Splice modulating oligonucleotides directed to exon 4 of Aph 1B	SEQ ID NO.
aaaagaaggacaaaucAAAGAC	662
aaagaaggacaaaucAAAGACC	663
aagaaggacaaaucAAAGACC	664
aagaaggacaaaucAAAGAC	665
agaaggacaaaucAAAGACC	666
agaaggacaaaucAAAGAC	667
gaaggacaaaucAAAGACC	668
aaggacaaaucAAAGACC	669
GAAACCUUAGUACUCACCUCA	670
AAACCUUAGUACUCACCUCA	671
AACCUUAGUACUCACCUCA	672
AACCUUAGUACUCACCUC	673
GAAACCUUAGUACUCACCUC	674
AACCUUAGUACUCACCUCAU	675
ACCUUAGUACUCACCUCAUA	676
CCUUAGUACUCACCUCAUAA	677
GAAACCUUAGUACUCACCU	678
AAACCUUAGUACUCACCUC	679
ACCUUAGUACUCACCUCAU	680
CCUUAGUACUCACCUCAUA	681
ACCUUAGUACUCACCUCA	682
CCUUAGUACUCACCUCAU	683
GGUCCGUGUCACCCGUAAGU	684
GUCCGUGUCACCCGUAAGUA	685
UCCGUGUCACCCGUAAGUAC	686
CCGUGUCACCCGUAAGUACC	687
GGUCCGUGUCACCCGUAAG	688
GUCCGUGUCACCCGUAAGU	689
UCCGUGUCACCCGUAAGUA	690
CCGUGUCACCCGUAAGUAC	691
CGUGUCACCCGUAAGUACC	692
GGUCCGUGUCACCCGUAA	693
GUCCGUGUCACCCGUAAG	694
UCCGUGUCACCCGUAAGU	695
CCGUGUCACCCGUAAGUA	696
CGUGUCACCCGUAAGUAC	697
GUGUCACCCGUAAGUACC	698
AUAAGUCcauacacagaguauc	699
UAAGUCcauacacagaguaucg	700
AAGUCcauacacagaguaucga	701
AGUCcauacacagaguaucgac	702
GUCcauacacagaguaucgaca	703
UCcauacacagaguaucgacag	704
Ccauacacagaguaucgacagu	705
AUAAGUCcauacacagaguau	706
UAAGUCcauacacagaguauc	707
AAGUCcauacacagaguaucg	708
AGUCcauacacagaguaucga	709
GUCcauacacagaguaucgac	710
UCcauacacagaguaucgaca	711
AUAAGUCcauacacagagua	712
UAAGUCcauacacagaguau	713
AAGUCcauacacagaguauc	714
AGUCcauacacagaguaucg	715
GUCcauacacagaguaucga	716
UCcauacacagaguaucgac	717
Ccauacacagaguaucgaca	718
AUAAGUCcauacacagagu	719
AAGUCcauacacagaguau	720
AGUCcauacacagaguauc	721
GUCcauacacagaguaucg	722
UCcauacacagaguaucga	723
Ccauacacagaguaucgac	724
GUCcauacacagaguauc	725
UCcauacacagaguaucg	726
Ccauacacagaguaucga	727
UAAGUCcauacac	728

E. HER3

The present invention further provides SMOs based on the sequences of HER3 (ERBB3; MIM 190151; 2065). These SMOs are used according to the methods of the invention to modulate splicing of HER3 pre-mRNA. In one embodiment, a SMO of the invention functions to decrease HER3 expression or function. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease HER3 expression or function. In one aspect, the SMO contacts a HER3 pre-mRNA and modulates the splicing of the HER3 pre-mRNA to favor expression of HER3Δ3, a variant in which exon 3 of HER3 is deleted and is, thus, non-functional. In another aspect, the SMO contacts a HER3 pre-mRNA and modulates the splicing of the HER3 pre-mRNA to favor expression of HER3Δ11, a variant in which exon 11 of HER3 is deleted and the mature protein is non-functional. In still another aspect, the SMO contacts a HER pre-mRNA and modulates splicing of the HER3 pre-mRNA to favor inclusion of intron 3 of HER3, thus enhancing expression of a truncated, non-functional protein.

Table 10 depicts exemplary SMOs for modulating splicing of HER3 pre-mRNA in order to either block a 3' splice site of exon 3 or include intron 3, thereby increasing expression of a truncated protein in a cell.

TABLE 10

3' to 5' Splice modulating oligonucleotides targeting exon 3 of HER3	SEQ ID NO.
CGGUCGAGGCGAACUGAGUCGAGU	729
UGAGUCGAGUGGCcagucaaggg	730
GGCGAACUGAGUCGAGUGGCca	731
GCGAACUGAGUCGAGUGGCcag	732
CGAACUGAGUCGAGUGGCcagu	733
GAACUGAGUCGAGUGGCcaguc	734
AACUGAGUCGAGUGGCcaguca	735
ACUGAGUCGAGUGGCcagucaa	736
CUGAGUCGAGUGGCcagucaag	737
UGAGUCGAGUGGCcagucaagg	738
GAGUCGAGUGGCcagucaaggg	739
GCGAACUGAGUCGAGUGGCca	740
CGAACUGAGUCGAGUGGCcag	741
GAACUGAGUCGAGUGGCcagu	742
AACUGAGUCGAGUGGCcaguc	743
ACUGAGUCGAGUGGCcaguca	744
CUGAGUCGAGUGGCcagucaa	745
UGAGUCGAGUGGCcagucaag	746
GAGUCGAGUGGCcagucaagg	747
AGUCGAGUGGCcagucaaggg	748
CGAACUGAGUCGAGUGGCca	749
GAACUGAGUCGAGUGGCcag	750
AACUGAGUCGAGUGGCcagu	751
ACUGAGUCGAGUGGCcaguc	752
CUGAGUCGAGUGGCcaguca	753
UGAGUCGAGUGGCcagucaa	754
GAGUCGAGUGGCcagucaag	755
AGUCGAGUGGCcagucaagg	756
GUCGAGUGGCcagucaaggg	757
GAACUGAGUCGAGUGGCca	758
AACUGAGUCGAGUGGCcag	759
ACUGAGUCGAGUGGCcagu	760
CUGAGUCGAGUGGCcaguc	761
UGAGUCGAGUGGCcaguca	762
GAGUCGAGUGGCcagucaa	763
AGUCGAGUGGCcagucaag	764
GUCGAGUGGCcagucaagg	765
UCGAGUGGCcagucaaggg	766
AACUGAGUCGAGUGGCca	767
ACUGAGUCGAGUGGCcag	768
CUGAGUCGAGUGGCcagu	769
UGAGUCGAGUGGCcaguc	770
GAGUCGAGUGGCcaguca	771
AGUCGAGUGGCcagucaa	772
GUCGAGUGGCcagucaag	773
UCGAGUGGCcagucaagg	774
CGAGUGGCcagucaaggg	775
ACUGAGUCGAGUGGCca	776
CUGAGUCGAGUGGCcag	777
UGAGUCGAGUGGCcagu	778
GAGUCGAGUGGCcaguc	779
AGUCGAGUGGCcaguca	780
GUCGAGUGGCcagucaa	781
UCGAGUGGCcagucaag	782
CGAGUGGCcagucaagg	783
GAGUGGCcagucaaggg	784
CUGAGUCGAGUGGCca	785
UGAGUCGAGUGGCcag	786
GAGUCGAGUGGCcagu	787
AGUCGAGUGGCcaguc	788
GUCGAGUGGCcaguca	789
UCGAGUGGCcagucaa	790
CGAGUGGCcagucaag	791
GAGUGGCcagucaagg	792
AGUGGCcagucaaggg	793
UGAGUCGAGUGGCca	794
GAGUCGAGUGGCcag	795
AGUCGAGUGGCcagu	796
GUCGAGUGGCcaguc	797

TABLE 10-continued

3' to 5' Splice modulating oligonucleotides targeting exon 3 of HER3	SEQ ID NO.
UCGAGUGGCcaguca	798
CGAGUGGCcagucaa	799
GAGUGGCcagucaag	800
AGUGGCcagucaagg	801
GUGGCcagucaaggg	802

Table 11 depicts exemplary SMOs for modulating splicing of HER3 pre-mRNA in order to exclude exon 11 thereby increasing expression of a non-functional protein in a cell.

TABLE 11

3' to 5' Splice modulating oligonucleotides directed to	SEQ ID NO.
cggagagagguuggggagucCAAU	803
ggggagucCAAUGGACUUGUAGGU	804
gggagucCAAUGGACUUGUAGGUC	805
cggagagagguuggggagucCAA	806
ggagucCAAUGGACUUGUAGGUC	807
cggagagagguuggggagucCA	808
gagucCAAUGGACUUGUAGGUC	809
agucCAAUGGACUUGUAGGUC	810
gucCAAUGGACUUGUAGGUC	811
ucCAAUGGACUUGUAGGUC	812
ucCAAUGGACUUGUAGGU	813

F. Cyclophilin D

The present invention further provides SMOs based on the sequences of CypD (PPID; MIM: 601753 GeneID: 5481). These SMOs are used according to the methods of the invention to modulate splicing of CypD pre-mRNA. In one embodiment, a SMO of the invention functions to decrease CypD expression or function. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease the CypD expression or function. In one aspect, the SMO contacts a CypD pre-mRNA and modulates the splicing of the CypD pre-mRNA to favor expression of CypDΔ1, a variant in which exon 1 of CypD is deleted and is, thus, non-functional. In another aspect, the SMO contacts an CypD pre-mRNA and modulates the splicing of the CypD pre-mRNA to favor expression of CypDΔ3, a variant in which exon 3 of CypD is deleted and is, thus, non-functional.

Table 12 depicts exemplary SMOs for modulating splicing of CypD pre-mRNA in order to exclude exon 1 thereby decreasing expression of a functional CypD protein in a cell.

TABLE 12

3' to 5' Splice modulating oligonucleotides directed to targeting exon 1 of CypD	SEQ ID NO.
UGCAGACGUUCAGUUCUACAGCGU	814
UGCAGACGUUCAGUUCUACAGCG	815
UGCAGACGUUCAGUUCUACAGC	816
UGCAGACGUUCAGUUCUACAG	817
UGCAGACGUUCAGUUCUACA	818
UGCAGACGUUCAGUUCUAC	819
AGACGUUCAGUUCUACAGCGUGGG	820
AGACGUUCAGUUCUACAGCGUGG	821
AGACGUUCAGUUCUACAGCGUG	822
AGACGUUCAGUUCUACAGCGU	823
AGACGUUCAGUUCUACAGCG	824
UGUAGCCUCCCCUCGCUCcacucg	825
GUAGCCUCCCCUCGCUCcacucg	826
UAGCCUCCCCUCGCUCcacucg	827
AGCCUCCCCUCGCUCcacucg	828
GCCUCCCCUCGCUCcacucg	829
CCUCCCCUCGCUCcacucg	830
CUGUAGCCUCCCCUCGCUCcacuc	831
UGUAGCCUCCCCUCGCUCcacuc	832
GUAGCCUCCCCUCGCUCcacuc	833
UAGCCUCCCCUCGCUCcacuc	834
AGCCUCCCCUCGCUCcacuc	835
GCCUCCCCUCGCUCcacuc	836
CCUGUACCUCCCCUCGCUCcacu	837
CUGUACCUCCCCUCGCUCcacu	838
UGUACCUCCCCUCGCUCcacu	839
GUACCUCCCCUCGCUCcacu	840
UACCUCCCCUCGCUCcacu	841
ACCUCCCCUCGCUCcacu	842
ACCUGUAGCCUCCCCUCGCUCcac	843
CCUGUAGCCUCCCCUCGCUCcac	844
CUGUAGCCUCCCCUCGCUCcac	845
UGUAGCCUCCCCUCGCUCcac	846
GUAGCCUCCCCUCGCUCcac	847
CACCUGUACCUCCCCUCGCUCca	848
ACCUGUACCUCCCCUCGCUCca	849
CCUGUACCUCCCCUCGCUCca	850
CUGUACCUCCCCUCGCUCca	851

TABLE 12-continued

3' to 5' Splice modulating oligonucleotides directed to targeting exon 1 of CypD	SEQ ID NO.
UGUACCUCCCCUCGCUCca	852
GCACCUGUAGCCUCCCCUCGCUCc	853
CACCUGUAGCCUCCCCUCGCUCc	854
ACCUGUAGCCUCCCCUCGCUCc	855
CCUGUAGCCUCCCCUCGCUCc	856
CUGUAGCCUCCCCUCGCUCc	857

Table 13 depicts exemplary SMOs for modulating splicing of CypD pre-mRNA in order to exclude exon 3 thereby decreasing expression of a functional CypD protein in a cell.

TABLE 13

3' to 5' Splice modulating oligonucleotides directed to targeting exon 3 of CypD	SEQ ID NO.
acaucAAUAAUUCUUUAAAUACUA	858
acaucAAUAAUUCUUUAAAUACU	859
acaucAAUAAUUCUUUAAAUAC	860
acaucAAUAAUUCUUUAAAUA	861
acaucAAUAAUUCUUUAAAU	862
acaucAAUAAUUCUUUAAA	863
caucAAUAAUUCUUUAAAUACUAA	864
caucAAUAAUUCUUUAAAUACUA	865
caucAAUAAUUCUUUAAAUACU	866
caucAAUAAUUCUUUAAAUAC	867
caucAAUAAUUCUUUAAAUA	868
caucAAUAAUUCUUUAAAU	869
aucAAUAAUUCUUUAAAUACUAAG	870
aucAAUAAUUCUUUAAAUACUAA	871
aucAAUAAUUCUUUAAAUACUA	872
aucAAUAAUUCUUUAAAUACU	873
aucAAUAAUUCUUUAAAUAC	874
aucAAUAAUUCUUUAAAUA	875
ucAAUAAUUCUUUAAAUACAAAGU	876
ucAAUAAUUCUUUAAAUACAAAG	877
ucAAUAAUUCUUUAAAUACAAA	878
ucAAUAAUUCUUUAAAUACAA	879
ucAAUAAUUCUUUAAAUACA	880
ucAAUAAUUCUUUAAAUAC	881
cAAUAAUUCUUUAAAUACUAAGUC	882
cAAUAAUUCUUUAAAUACUAAGU	883
cAAUAAUUCUUUAAAUACUAAG	884
cAAUAAUUCUUUAAAUACUAA	885
cAAUAAUUCUUUAAAUACUA	886
cAAUAAUUCUUUAAAUAC	887
UUUAGUCUUACCCUGUCCACCUCU	888
UUAGUCUUACCCUGUCCACCUCU	889
UAGUCUUACCCUGUCCACCUCU	890
AGUCUUACCCUGUCCACCUCU	891
AGUCUUACCCUGUCCACCUC	892
AGUCUUACCCUGUCCACCU	893
GUCUUACCCUGUCCACCUCUUUCA	894
UCUUACCCUGUCCACCUCUUUCA	895
CUUACCCUGUCCACCUCUUUCA	896
UUACCCUGUCCACCUCUUUCA	897
UACCCUGUCCACCUCUUUCA	898
ACCCUGUCCACCUCUUUCA	899
ACUUUUUAAACUUCUACUUU	900
UUCUACUUUUAAAGGUAAUGUUCc	901
UCUACUUUUAAAGGUAAUGUUCc	902
CUACUUUUAAAGGUAAUGUUCc	903
UACUUUUAAAGGUAAUGUUCc	904
ACUUUUAAAGGUAAUGUUCc	905
CUUUUAAAGGUAAUGUUCc	906
CUACUUUUAAAGGUAAUGUUCca	907
UACUUUUAAAGGUAAUGUUCca	908
ACUUUUAAAGGUAAUGUUCca	909
CUUUUAAAGGUAAUGUUCca	910
UUUUAAAGGUAAUGUUCca	911
UUUAAAGGUAAUGUUCca	912
CUACUUUUAAAGGUAAUGUUCcau	913
UACUUUUAAAGGUAAUGUUCcau	914
ACUUUUAAAGGUAAUGUUCcau	915
CUUUUAAAGGUAAUGUUCcau	916
UUUUAAAGGUAAUGUUCcau	917
UUUAAAGGUAAUGUUCcau	918

G. FOXM1

The present invention further provides SMOs based on the sequences of FOXM1 (FOXM1; MIM: 602341; GeneID: 2305). These SMOs are used according to the methods of the invention to modulate splicing of FOXM1 pre-mRNA. In one embodiment, a SMO of the invention functions to decrease FOXM1 expression. In another embodiment, the invention includes a pharmaceutical composition comprising a SMO of the invention, where the pharmaceutical composition of the invention comprises a SMO that functions to decrease the FOXM1 expression. In one aspect, the SMO contacts a FOXM1 pre-mRNA and modulates the splicing of the FOXM1 pre-mRNA to favor expression of FOXM1Δ3, a variant in which exon 3 of FOXM1 D is excluded. In another aspect, the SMO contacts an FOXM1 pre-mRNA and modulates the splicing of the FOXM1 pre-mRNA to favor expression of FOXM1Δ6, a variant in which exon 6 of FOXM1 is excluded.

Table 14 depicts exemplary SMOs for modulating splicing of FOXM1 pre-mRNA in order to exclude exon 3 thereby decreasing expression of a functional FOXM1 protein in a cell.

TABLE 14

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 3 of FOXM1	SEQ ID NO.
GUAGGUCACCGAAGCUUUCUAC	919
GUAGGUCACCGAAGCUUUCUA	920
GUAGGUCACCGAAGCUUUCU	921
CCUCUUAACAGUGGACCUCGUC	922
CCUCUUAACAGUGGACCUCGU	923
CUCUUAACAGUGGACCUCGU	924
CUCUUAACAGUGGACCUCG	925
CUCUUAACAGUGGACCUC	926
ACCUCGUCGCUGUCCAAUUCca	927
CCUCGUCGCUGUCCAAUUCcau	928
CUCGUCGCUGUCCAAUUCcacu	929
UCGUCGCUGUCCAAUUCcacuu	930
CCUCGUCGCUGUCCAAUUCca	931
CUCGUCGCUGUCCAAUUCcac	932
UCGUCGCUGUCCAAUUCcacu	933
CGUCGCUGUCCAAUUCcacuu	934
GUCGCUGUCCAAUUCcacuua	935
UCGCUGUCCAAUUCcacuuaa	936
CUCGUCGCUGUCCAAUUCca	937
UCGUCGCUGUCCAAUUCcac	938
CGUCGCUGUCCAAUUCcacu	939
GUCGCUGUCCAAUUCcacuu	940
UCGCUGUCCAAUUCcacuua	941
CGCUGUCCAAUUCcacuuaa	942
UCGUCGCUGUCCAAUUCca	943
CGUCGCUGUCCAAUUCcac	944
GUCGCUGUCCAAUUCcacu	945

TABLE 14-continued

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 3 of FOXM1	SEQ ID NO.
UCGCUGUCCAAUUCcacuu	946
CGCUGUCCAAUUCcacuua	947
GCUGUCCAAUUCcacuuaa	948
CGUCGCUGUCCAAUUCca	949
GUCGCUGUCCAAUUCcac	950
UCGCUGUCCAAUUCcacu	951
CGCUGUCCAAUUCcacuu	952
GCUGUCCAAUUCcacuua	953

Table 15 depicts exemplary SMOs for modulating splicing of FOXM1 pre-mRNA in order to exclude exon 6 decreasing expression of a functional FOXM1 protein in a cell.

TABLE 15

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 6 of FOXM1	SEQ ID NO.
GGCGGUGGUCGGCGGUGGUCGG	954
GGCGGUGGUCGGCGGUGGUCGGU	955
GGCGGUGGUCGGCGGUGGUCGG	956
GGCGGUGGUCGGCGGUGGUCG	957
GGCGGUGGUCGGCGGUGGUC	958
GGCGGUGGUCGGCGGUGGU	959
cGGCGGUGGUCGGUGACCUGGGUC	960
cGGCGGUGGUCGGUGACCUGGGU	961
cGGCGGUGGUCGGUGACCUGGG	962
cGGCGGUGGUCGGUGACCUGG	963
cGGCGGUGGUCGGUGACCUG	964
cGGCGGUGGUCGGUGACCU	965
ccGGCGGUGGUCGGCGGUGGUCGG	966
ccGGCGGUGGUCGGCGGUGGUCG	967
ccGGCGGUGGUCGGCGGUGGUC	968
ccGGCGGUGGUCGGCGGUGGU	969
ccGGCGGUGGUCGGCGGUGG	970
ccGGCGGUGGUCGGCGGUG	971
accGGCGGUGGUCGGCGGUGGUCG	972
accGGCGGUGGUCGGCGGUGGUC	973
accGGCGGUGGUCGGCGGUGGU	974
accGGCGGUGGUCGGCGGUGG	975
accGGCGGUGGUCGGCGGUG	976
accGGCGGUGGUCGGCGGU	977

TABLE 15-continued

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 6 of FOXM1	SEQ ID NO.
gaccGGCGGUGGUCGGCGGUGGUC	978
gaccGGCGGUGGUCGGCGGUGGU	979
gaccGGCGGUGGUCGGCGGUGG	980
gaccGGCGGUGGUCGGCGGUG	981
gaccGGCGGUGGUCGGCGGU	982
gaccGGCGGUGGUCGGCGG	983
ggaccGGCGGUGGUCGGCGGUGGU	984
ggaccGGCGGUGGUCGGCGGUGG	985
ggaccGGCGGUGGUCGGCGGUG	986
ggaccGGCGGUGGUCGGCGGU	987
ggaccGGCGGUGGUCGGCGG	988
ggaccGGCGGUGGUCGGCG	989
cggaccGGCGGUGGUCGGCGGUGG	990
cggaccGGCGGUGGUCGGCGGUG	991
cggaccGGCGGUGGUCGGCGGU	992
cggaccGGCGGUGGUCGGCGG	993
cggaccGGCGGUGGUCGGCG	994
cggaccGGCGGUGGUCGGC	995
CGGUGGUCGGUGACCUGGGUCCCA	996
CGGUGGUCGGUGACCUGGGUCCC	997
CGGUGGUCGGUGACCUGGGUCC	998
CGGUGGUCGGUGACCUGGGUC	999
CGGUGGUCGGUGACCUGGGU	1000
GGUGGUCGGUGACCUGGGUCCCAG	1001
GGUGGUCGGUGACCUGGGUCCCA	1002
GGUGGUCGGUGACCUGGGUCCC	1003
GGUGGUCGGUGACCUGGGUCC	1004
GGUGGUCGGUGACCUGGGUC	1005
GUGGUCGGUGACCUGGGUCCCAGA	1006
GUGGUCGGUGACCUGGGUCCCAG	1007
GUGGUCGGUGACCUGGGUCCCA	1008
GUGGUCGGUGACCUGGGUCCC	1009
GUGGUCGGUGACCUGGGUCC	1010
UGGGUCCCAGAGGUGUUAACGGGC	1011
UGGGUCCCAGAGGUGUUAACGGG	1012
UGGGUCCCAGAGGUGUUAACGG	1013
UGGGUCCCAGAGGUGUUAACG	1014
UGGGUCCCAGAGGUGUUAAC	1015

TABLE 15-continued

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 6 of FOXM1	SEQ ID NO.
GGGUCCCAGAGGUGUUAACGGGCU	1016
GGGUCCCAGAGGUGUUAACGGGC	1017
GGGUCCCAGAGGUGUUAACGGG	1018
GGGUCCCAGAGGUGUUAACGG	1019
GGGUCCCAGAGGUGUUAACG	1020
CCCAGAGGUGUUAACGGGCUCGUG	1021
CCCAGAGGUGUUAACGGGCUCGU	1022
CCCAGAGGUGUUAACGGGCUCG	1023
CCCAGAGGUGUUAACGGGCUC	1024
CCCAGAGGUGUUAACGGGCU	1025
AGAGGUGUUAACGGGCUCGUGAAC	1026
AGAGGUGUUAACGGGCUCGUGAA	1027
AGAGGUGUUAACGGGCUCGUGA	1028
AGAGGUGUUAACGGGCUCGUG	1029
AGAGGUGUUAACGGGCUCGU	1030
GAGGUGUUAACGGGCUCGUGAACC	1031
GAGGUGUUAACGGGCUCGUGAAC	1032
GAGGUGUUAACGGGCUCGUGAA	1033
GAGGUGUUAACGGGCUCGUGA	1034
GAGGUGUUAACGGGCUCGUG	1035
GUUAACGGGCUCGUGAACCUUAGU	1036
GUUAACGGGCUCGUGAACCUUAG	1037
GUUAACGGGCUCGUGAACCUUA	1038
GUUAACGGGCUCGUGAACCUU	1039
GUUAACGGGCUCGUGAACCU	1040
GUUAACGGGCUCGUGAACC	1041
UUAACGGGCUCGUGAACCUUAGUc	1042
UAACGGGCUCGUGAACCUUAGUc	1043
AACGGGCUCGUGAACCUUAGUc	1044
ACGGGCUCGUGAACCUUAGUc	1045
CGGGCUCGUGAACCUUAGUc	1046
GGGCUCGUGAACCUUAGUc	1047
UAACGGGCUCGUGAACCUUAGUca	1048
AACGGGCUCGUGAACCUUAGUca	1049
ACGGGCUCGUGAACCUUAGUca	1050
CGGGCUCGUGAACCUUAGUca	1051
GGGCUCGUGAACCWAGUca	1052
GGCUCGUGAACCUUAGUca	1053

TABLE 15-continued

3' to 5' Splice modulating oligonucleotides directed to targeting Exon 6 of FOXM1	SEQ ID NO.
AACGGGCUCGUGAACCUUAGUcau	1054
ACGGGCUCGUGAACCUUAGUcau	1055
CGGGCUCGUGAACCUUAGUcau	1056
GGGCUCGUGAACCUUAGUcau	1057
GGCUCGUGAACCUUAGUcau	1058
GCUCGUGAACCUUAGUcau	1059
ACGGGCUCGUGAACCUUAGUcauu	1060
CGGGCUCGUGAACCUUAGUcauu	1061
GGGCUCGUGAACCUUAGUcauu	1062
GGCUCGUGAACCUUAGUcauu	1063
GCUCGUGAACCUUAGUcauu	1064
CUCGUGAACCUUAGUcauu	1065
CGGGCUCGUGAACCUUAGUcauuc	1066
GGGCUCGUGAACC'UUAGUcauuc	1067
GGCUCGUGAACCUUAGUcauuc	1068
GCUCGUGAACCUUAGUcauuc	1069
CUCGUGAACCUUAGUcauuc	1070
UCGUGAACCUUAGUcauuc	1071
GGGCUCGUGAACCUUAGUcauucc	1072
GGCUCGUGAACCUUAGUcauucc	1073
GCUCGUGAACCUUAGUcauucc	1074
CUCGUGAACCUUAGUcauucc	1075
UCGUGAACCUUAGUcauucc	1076
CGUGAACCUUAGUcauucc	1077
GGCUCGUGAACCUUAGUcauucca	1078
GCUCGUGAACCUUAGUcauucca	1079
CUCGUGAACCUUAGUcauucca	1080
UCGUGAACCUUAGUcauucca	1081
CGUGAACCUUAGUcauucca	1082
GUGAACCUUAGUcauucca	1083
GCUCGUGAACCUUAGUcauuccaa	1084
CUCGUGAACCUUAGUcauuccaa	1085
UCGUGAACCUUAGUcauuccaa	1086
CGUGAACCUUAGUcauuccaa	1087
GUGAACCUUAGUcauuccaa	1088
UGAACCUUAGUcauuccaa	1089

It will be appreciated by the skilled artisan that a SMO useful in practicing the methods of the invention should not be considered to be limited to those SMO sequences explicitly recited herein, but rather should be considered to include any SMO sufficiently complementary to a target pre-mRNA in such a way as to modulate its splicing. The invention also encompasses all derivatives, variants, and modifications of the SMOs of the invention, as described elsewhere herein.

Oligonucleotides of the invention are of any size and/or chemical composition sufficient to specifically bind to a target RNA (e.g., pre-mRNA). In exemplary embodiments, the oligonucleotides of the invention are oligonucleotides of between about 5-300 nucleotides (or modified nucleotides), preferably between about 10-100 nucleotides (or modified nucleotides; e.g., ribonucleotides or modified ribonucleotides), for example, between about 15-35, e.g., about 15-20, 20-25, 25-30, 30-35 (31, 32, 33, 34, 35), or 35-40 nucleotides (or modified nucleotides; e.g., ribonucleotides or modified ribonucleotides).

Synthesis of SMOs

An oligonucleotide of the invention, i.e. the SMO, can be synthesized using any procedure known in the art, including chemical synthesis, enzymatic ligation, organic synthesis, and biological synthesis.

In one embodiment, an RNA molecule, e.g., SMO, is prepared chemically. Methods of synthesizing RNA and DNA molecules are known in the art, in particular, the chemical synthesis methods as described in Verma and Eckstein (1998) Annul Rev. Biochem. 67:99-134. RNA can be purified from a mixture by extraction with a solvent or resin, precipitation, electrophoresis, chromatography, or a combination thereof. Alternatively, the RNA may be used with no or a minimum of purification to avoid losses due to sample processing.

Modifications of SMOs

In a preferred aspect, the oligonucleotides of the present invention (i.e. SMOs) are modified to improve stability in serum or growth medium for cell cultures, or otherwise to enhance stability during delivery to subjects and/or cell cultures. In order to enhance the stability, the 3'-residues may be stabilized against degradation, e.g., they may be selected such that they consist of purine nucleotides, particularly adenosine or guanosine nucleotides. Alternatively, substitution of pyrimidine nucleotides by modified analogues, e.g., substitution of uridine by 2'-deoxythymidine can be tolerated without affecting the efficiency of oligonucleotide reagent-induced modulation of splice site selection. For example, the absence of a 2' hydroxyl may significantly enhance the nuclease resistance of the oligonucleotides in tissue culture medium.

In an embodiment of the present invention the oligonucleotides, e.g., SMOs, may contain at least one modified nucleotide analogue. The nucleotide analogues may be located at positions where the target-specific activity, e.g., the splice site selection modulating activity is not substantially effected, e.g., in a region at the 5'-end and/or the 3'-end of the oligonucleotide molecule. Particularly, the ends may be stabilized by incorporating modified nucleotide analogues.

Preferred nucleotide analogues include sugar- and/or backbone-modified ribonucleotides (i.e., include modifications to the phosphate-sugar backbone). For example, the phosphodiester linkages of natural RNA may be modified to include at least one of a nitrogen or sulfur heteroatom. In preferred backbone-modified ribonucleotides the phosphoester group connecting to adjacent ribonucleotides is replaced by a modified group, e.g., of phosphothioate group. In preferred sugar-modified ribonucleotides, the 2' OH-group is replaced by a group selected from CH_3, H, OR, R, halo, SH, SR, NH_2, NHR, NR_2 or ON, wherein R is C_1-C_6 alkyl, alkenyl or alkynyl and halo is F, Cl, Br or I. In a preferred embodiment, the 2' OH-group is replaced by CH_3.

Also preferred are nucleobase-modified ribonucleotides, i.e., ribonucleotides, containing at least one non-naturally occurring nucleobase instead of a naturally occurring nucleobase. Bases may be modified to block the activity of adenosine deaminase. Exemplary modified nucleobases include, but are not limited to phosphorothioate derivatives and acridine substituted nucleotides, 2'O-methyl substitutions, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N-6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine, uridine and/or cytidine modified at the 5-position, e.g., 5-(2-amino)propyl uridine, 5-bromo uridine; adenosine and/or guanosines modified at the 8 position, e.g., 8-bromo guanosine; deaza nucleotides, e.g., 7-deaza-adenosine; O- and N-alkylated nucleotides, e.g., N6-methyl adenosine. It should be noted that the above modifications may be combined. Oligonucleotides of the invention also may be modified with chemical moieties (e.g., cholesterol) that improve the in vivo pharmacological properties of the oligonucleotides.

Within the oligonucleotides (e.g., oligoribonucleotides) of the invention, as few as one and as many as all nucleotides of the oligonucleotide can be modified. For example, a 20-mer oligonucleotide (e.g., oligoribonucleotide) of the invention may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 modified nucleotides. In preferred embodiments, the modified oligonucleotides (e.g., oligoribonucleotides) of the invention will contain as few modified nucleotides as are necessary to achieve a desired level of in vivo stability and/or bioaccessibility while maintaining cost effectiveness. An SMOs of the invention include oligonucleotides synthesized to include any combination of modified bases disclosed herein in order to optimize function. In one embodiment, a SMO of the invention comprises at least two different modified bases. In another embodiment, a SMO of the invention may comprise alternating 2'O-methyl substitutions and LNA bases.

An oligonucleotide of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α-units, the strands run parallel to each other (Gaultier et al., 1987, Nucleic Acids Res. 15:6625-6641). The oligonucleotide can also comprise a 2'-o-methylribonucleotide (Inoue et al., 1987, Nucleic Acids Res. 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

In various embodiments, the oligonucleotides of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acid molecules (see Hyrup et al., 1996, Bioorganic & Medicinal Chemistry 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), supra; Perry-O'Keefe et al. (1996) Proc. Natl. Acad. Sci. USA 93:14670-675.

In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, supra). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), supra, and Finn et al. (1996) Nucleic Acids Res. 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramiditea coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl) amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al., 1989, Nucleic Acids Res. 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al., 1996, Nucleic Acids Res. 24(17): 3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al., 1975, Bioorganic Med. Chem. Lett. 5: 1119-11124).

The oligonucleotides of the invention can also be formulated as morpholino oligonucleotides. In such embodiments, the riboside moiety of each subunit of an oligonucleotide of the oligonucleotide is converted to a morpholine moiety (morpholine=C_4H_9NO; refer to Heasman, J. 2002 Developmental Biology 243, 209-214, the entire contents of which are incorporated herein by reference).

A further preferred oligonucleotide modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methelyne $(—CH_2—)_n$ group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226, the entire contents of which are incorporated by reference herein.

In other embodiments, the oligonucleotide can include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, e.g., PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, Bio/Techniques 6:958-976) or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acid molecules having at least one region which is complementary to a nucleic acid molecule of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid molecule of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid molecule comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid molecules are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acid molecules are described, for example, in U.S. Pat. No. 5,876,930.

The target RNA (e.g., pre-mRNA) splice-modifying reaction guided by oligonucleotides of the invention is highly sequence specific. In general, oligonucleotides containing nucleotide sequences perfectly complementary to a portion of the target RNA are preferred for blocking of the target RNA. However, 100% sequence complementarity between the oligonucleotide and the target RNA is not required to practice the present invention. Thus, the invention may tolerate sequence variations that might be expected due to genetic mutation, strain polymorphism, or evolutionary divergence. For example, oligonucleotide sequences with insertions, deletions, and single point mutations relative to the target sequence may also be effective for inhibition. Alternatively, oligonucleotide sequences with nucleotide analog substitutions or insertions can be effective for blocking.

Greater than 70% sequence identity (or complementarity), e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% sequence identity, and any and all whole or partial increments there between the oligonucleotide and the target RNA, e.g., target pre-mRNA, is preferred.

Sequence identity, including determination of sequence complementarity for nucleic acid sequences, may be determined by sequence comparison and alignment algorithms known in the art. To determine the percent identity of two nucleic acid sequences (or of two amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). The nucleotides (or amino acid residues) at corresponding nucleotide (or amino acid) positions are then compared. When a position in the first sequence is occupied by the same residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=number of identical positions/total number of positions×100), optionally penalizing the score for the number of gaps introduced and/or length of gaps introduced.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment, the alignment generated over a certain portion of the sequence aligned having sufficient identity but not over portions having low degree of identity (i.e., a local alignment). A preferred, non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-68, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-77. Such an algorithm is incorporated into the BLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10.

In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the length of the aligned sequences (i.e., a gapped alignment). To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25(17):3389-3402. In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the entire length of the sequences aligned (i.e., a global alignment). A preferred, non-limiting example of a mathematical algorithm utilized for the global comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Alternatively, the oligonucleotide may be defined functionally as a nucleotide sequence (or oligonucleotide sequence) a portion of which is capable of hybridizing with the target RNA (e.g., 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50° C. or 70° C. hybridization for 12-16 hours; followed by washing). Additional preferred hybridization conditions include hybridization at 70° C. in 1×SSC or 50° C. in 1×SSC, 50% formamide followed by washing at 70° C. in 0.3×SSC or hybridization at 70° C. in 4×SSC or 50° C. in 4×SSC, 50% formamide followed by washing at 67° C. in 1×SSC. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10° C. less than the melting temperature (Tm) of the hybrid, where Tm is determined according to the following equations. For hybrids less than 18 base pairs in length, Tm(° C.)=2(number of A+T bases)+4(number of G+C bases). For hybrids between 18 and 49 base pairs in length, Tm(° C.)=81.5+16.6 (log 10[Na$^+$])+0.41(% G+C)−(600/N), where N is the number of bases in the hybrid, and [Na$^+$] is the concentration of sodium ions in the hybridization buffer ([Na$^+$] for 1×SSC=0.165 M). Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, et al., 2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F. M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference. The length of the identical nucleotide sequences may be at least about 10, 12, 15, 17, 20, 22, 25, 27, 30, 32, 35, 37, 40, 42, 45, 47 or 50 bases.

II. Methods

The present invention provides compositions and methods for modulating pre-mRNA splicing using a SMO of the invention to abrogate disease-causing mutations in a protein. An SMO of the invention may modulate pre-mRNA splicing by blocking cryptic splice sites, removing an exon, including an exon, or shifting the reading frame of the pre-mRNA in order to alter protein isoform expression.

Accordingly, the present invention provides compositions and methods of treating a subject at risk of, susceptible to, or having a disease, disorder, or condition associated with aberrant or unwanted target pre-mRNA expression or function. In one embodiment, a target pre-mRNA of the invention is any aberrantly spliced or unwanted pre-mRNA encoding a protein that results in, causes, produces, or pre-disposes a subject to a disease or disorder. In another embodiment, aberrant splicing of a target pre-mRNA if the invention is not a cause of a disease or disorder, but modulation of the target pre-mRNA reduces at least one symptom of the disease or disorder.

In another embodiment, the invention provides a method of preventing in a subject, a disease, disorder, or condition associated with aberrant or unwanted pre-mRNA splicing of a protein and altered protein expression or function, the method comprising administering to the subject a pharmaceutical composition comprising a SMO, or vector, or transgene encoding same.

A target pre-mRNA of the invention is any pre-mRNA that is abnormally spliced or a pre-mRNA whose altered activity is likely to have a beneficial effect on a subject. In one embodiment, a target pre-mRNA of the invention comprises a 5-HT2C receptor. In yet another embodiment, a target pre-mRNA of the invention is an aberrantly spliced 5-HT2CR pre-mRNA in a subject that results in a truncated, non-functional 5-HT2C receptor.

In yet another embodiment, a target pre-mRNA of the invention is an AMPA glutamate receptor (GluR) subunit comprising GluR1, GluR2, Glur3, GluR4, or any combination thereof. In a further embodiment, a target pre-mRNA of the invention is an AMPA glutamate receptor (GluR) subunit comprising GluR1, GluR2, Glur3, GluR4, or any combination thereof where it is desirable to alter the ratio of flip and flop isoforms of any one of, or any combination of these GluRs. In yet another embodiment, a target pre-mRNA of the invention is an aberrantly spliced GluR pre-mRNA in a subject that results in a truncated, non-functional glutamate receptor.

In still another embodiment, a target pre-mRNA of the invention is OGA.

In yet another embodiment of the invention, a target pre-mRNA of the invention is Aph1B. In another embodiment, a target pre-mRNA of the invention is HER3. In still another embodiment, a target pre-mRNA of the invention is FOXM1. In yet another embodiment, a target pre-mRNA of the invention is CypD.

Subjects at risk for a disease which is caused or contributed to by aberrant or unwanted target pre-mRNA expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays known in the art. Administration of a prophylactic agent comprising a SMO can occur prior to the manifestation of symptoms characteristic of the target pre-mRNA aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression.

The invention encompasses methods of modulating target pre-mRNA splicing and thus expression or activity of the specified protein for therapeutic purposes. In an exemplary embodiment, the modulatory method of the invention involves contacting a cell capable of expressing a target pre-mRNA with a pharmaceutical composition comprising a SMO or vector or transgene encoding same, that is specific for the target pre-mRNA (e.g., is specific for the pre-mRNA) such that expression or one or more of the activities of target pre-mRNA is modulated. These modulatory methods can be performed in vitro (e.g., by culturing the cell with the agent) or, alternatively, in vivo (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating a subject afflicted with a disease or disorder characterized by aberrant splicing of a target pre-mRNA molecule resulting in deleterious protein expression or activity.

A. Method of Modulating 5-HT2C Receptor Pre-mRNA Splicing

In one embodiment, the present invention provides a method of modulating 5-HT2C receptor pre-mRNA splicing using a SMO to mimic the function of the snoRNA, HBII-52, in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts 5-HT2CR pre-mRNA and modulates the splicing of the 5-HT2CR pre-mRNA to include exon 5b in the mature mRNA.

Diseases and disorders where increasing 5-HT2CR expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, PWS and Angelman Syndrome (Kishore et al., 2006, Cold Spring Harbor Symp. Quant. Biol. 71: 329-334; Kishore et al., 2006, Science, 311: 230-232; Sridhar et al., 2008, J. Biomed. Sci., 15: 697-705); hyperphagia induced obesity (Dunlop et al., 2006, CNS Drug Rev., 12: 167-177; Nilsson, 2006, J. Med. Chem., 49: 4023-4034); obsessive/compulsive disorder (Flaisher-Grinberg et al., 2008, Int. J. Neuropsychopharmacology, 11: 811-825); depression, including psychotic depression, major depressive disorder, bipolar disorder (Rosenzweig-Lipson et al., 2007, Psychopharmacology (Berl), 192: 159-170; Dunlop et al., 2006, CNS Drug Rev., 12: 167-177; Rosenzweig-Lipson et al., 2007, Drug News Perspect., 20: 565-571); sleep impairment (Monti et al., 2008, Prog. Brain Res., 172: 625-646); autism (Tandon et al., 2008, Mol. Med., 105: 79-84); epilepsy (Bagdy et al., 2007, J. Neurochem., 100: 857-873; Tupal et al., 2006, Epilepsia, 47: 21-26); schizophrenia (Rosenzweig-Lipson et al., 2007, Drug News Perspect., 20: 565-571); Parkinson's disease (Di et al., 2006, Curr. Med. Chem., 13: 3069-3081); drug addiction (Bubar et al., 2008, Prog. Brain Res., 172: 319-346); spinal cord injury or traumatic brain injury (Kao et al., 2006, Brain Res., 1112: 159-168); neuopathic pain (Nakae et al., 2008, Eur. J. Neurosci. 27: 2373-2379; Nakae et al., 2008, Neurosci. Res., 60: 228-231); diabetes (Wade et al., 2008, Endocrinology, 149: 955-961); Alzheimer's disease (Pritchard et al., 2008, Neurobiol. Aging, 29: 341-347; Arjona et al., 2002, Brain Res., 951: 135-140), and chronic pain.

In another embodiment, the present invention provides a method of treating a subject afflicted with PWS. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject afflicted with PWS, wherein the SMO contacts 5-HT2CR pre-mRNA and modulates the splicing of the 5-HT2CR pre-mRNA to include exon 5b from the mRNA, thereby resulting in expression of a full-length, functional 5-HT2CR protein in the subject.

In yet another embodiment, the present invention provides a method of treating a subject afflicted with a 5-HT2CR splicing defect, where the defect results in a non-functional truncated 5-HT2C receptor that includes exon 5a, but not exon 5b. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention to a subject afflicted with a 5-HT2CR splicing defect, wherein the SMO contacts 5-HT2CR pre-mRNA and modulates the splicing of the 5-HT2CR pre-mRNA, thereby resulting in expression of a full-length, functional 5-HT2CR protein in the subject.

In still another embodiment, the present invention provides a method of treating a subject afflicted with hyperphagia. In one aspect, the hyperphagia is caused by a 5-HT2CR splicing defect. In another aspect, the hyperphagia is not caused by a 5-HT2CR splicing defect, but the subject afflicted with hyperphagia experiences a therapeutic benefit from increasing expression of the 5-HT2CR. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject afflicted with hyperphagia, wherein the SMO contacts 5-HT2CR pre-mRNA and modulates the splicing of the 5-HT2CR pre-mRNA, thereby resulting in increased expression of a full-length, functional 5-HT2CR protein and reducing hyperphagia in the subject.

In yet another embodiment, the present invention provides a method of treating a subject afflicted with obsessive-compulsive disorder (OCD), or a subject afflicted with the symptoms of OCD, In one aspect, the OCD is caused by a 5-HT2CR splicing defect. In another aspect, the OCD is not caused by a 5-HT2CR splicing defect, but the subject afflicted with OCD experiences a therapeutic benefit from increasing expression of the 5-HT2CR. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject afflicted with OCD, wherein the SMO contacts 5-HT2CR pre-mRNA and modulates the splicing of the 5-HT2CR pre-mRNA, thereby resulting in expression of a full-length, functional 5-HT2CR protein and a reductions of the symptoms of OCD in the subject.

B. Method of Modulating GluR Receptor Pre-mRNA Splicing

In one embodiment, the present invention provides a method of treating a subject afflicted with a GluR splicing defect, where the defect results in a non-functional GluR. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention to a subject afflicted with a GluR splicing defect, wherein the SMO contacts GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA, thereby resulting in expression of a full-length, functional GluR protein in the subject. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

In another embodiment, the present invention provides a method of modulating splicing of a GluR receptor pre-mRNA using a SMO to decrease the GluR flip isoform expression in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a GluR pre-mRNA and modulates the splicing of the GluR to decrease the GluR flip isoform expression and in the subject. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

In yet another embodiment, the present invention provides a method of treating a subject afflicted with a GluR splicing defect, where the deficit results in a decreased flip:flop isoform ratio for a GluR subunit. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject afflicted with an abnormal flip:flop ratio, wherein the SMO contacts GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA, thereby resulting in decreased flip:flop isoform ratio for a GluR subunit. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

In still another embodiment, the present invention provides a method of treating a subject afflicted with amyotrophic lateral sclerosis (ALS; Sandyk, R., 2006, Int. J. Neurosci. 116: 775-826; Ionov, I. D., 2007, Amyotroph. Lateral Scler. 8:260-265). The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA to decrease the GluR flip isoform expression and/or decrease the GluR flip/flop isoform ratio in the subject.

In another embodiment, the present invention provides a method of treating a subject afflicted with epilepsy. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA to decrease the GluR flip isoform expression and/or decrease the GluR flip/flop isoform ratio.

In yet another embodiment, the present invention provides a method of decreasing neuronal excitability in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention to a subject afflicted with neuronal excitotoxity, wherein the SMO contacts GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA, thereby resulting in decreased flip:flop isoform ratio for a GluR subunit. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

In yet another embodiment, the present invention provides a method of decreasing a Ca^{2+}-conductance through a GluR in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention to a subject, wherein the SMO contacts GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA, thereby resulting in a decreased Ca^{2+}-conductance through an AMPA channel in a subject. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

In yet another embodiment, the present invention provides a method of increasing GluR desensitization in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention to a subject, wherein the SMO contacts GluR pre-mRNA and modulates the splicing of the GluR pre-mRNA to decrease the GluR flip isoform expression and/or decrease the GluR flip/flop isoform ratio, thereby resulting in a increased AMPA channel desensitization in a subject. A skilled artisan will appreciate that the method may be used to modulate splicing of a GluR1, GluR2, GluR3, or Glur4 subunit, as well as any combination thereof.

C. Method of Modulating OGA Receptor Pre-mRNA Splicing

In another embodiment, the present invention provides a method of modulating splicing of OGA pre-mRNA using a SMO to decrease expression or functionality of OGA in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts an OGA pre-mRNA and modulates the splicing of the OGA pre-mRNA to favor expression of naturally occurring splice variants which have reduced catalytic activity. In one aspect, an alternative splice variant of OGA with reduced catalytic activity comprises OGA10t, a read through variant which results in 15 amino acids being added from intron 10. In another aspect, the method comprises administering a SMO of the invention, or a pharmaceutical composition comprising a SMO of the invention, to a subject, wherein the SMO contacts an OGA pre-mRNA and modulates the splicing of the OGA pre-mRNA to favor expression of a non-natural alternative splice variant of OGA with reduced catalytic activity. In one aspect, an alternative splice variant of OGA with reduced catalytic activity comprises OGAΔ10 wherein exon 10 of the gene is excluded. In another aspect, an alternative splice variant of OGA with reduced catalytic activity comprises OGAΔ8 wherein exon 8 of the OGA gene is excluded. Diseases and disorders where decreasing OGA expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, Alzheimer's Disease.

In another embodiment, the present invention provides a method of treating a subject afflicted with Alzheimer's Disease. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts an OGA pre-mRNA and modulates the splicing of the OGA pre-mRNA to favor expression of naturally occurring splice variants which have reduced catalytic activity, as described elsewhere herein.

D. Method of Modulating Aph1B Receptor Pre-mRNA Splicing

In one embodiment, the present invention provides a method of modulating splicing of Aph1B pre-mRNA using a SMO to decrease expression or functionality of Aph1B in a subject. The method comprises administering a SMO of the invention, or a pharmaceutical composition comprising a SMO of the invention, to a subject, wherein the SMO contacts an Aph1B pre-mRNA and modulates the splicing of the Aph1B pre-mRNA to favor expression of Aph1BΔ4, a variant in which exon 4 of Aph1B is deleted and is, thus, non-functional. Diseases and disorders where increasing Aph1B expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, Alzheimer's Disease.

In another embodiment, the present invention provides a method of treating a subject afflicted with Alzheimer's Disease. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts an Aph1B pre-mRNA and modulates the splicing of the Aph1B pre-mRNA to favor expression of Aph1BΔ4, as described elsewhere herein.

E. Method of Modulating FOXM1 Receptor Pre-mRNA Splicing

In another embodiment, the present invention provides a method of modulating splicing of FOXM1 pre-mRNA using a SMO to decrease expression or functionality of FOXM1 in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a FOXM1 pre-mRNA and modulates the splicing of the Aph1B pre-mRNA to favor expression of FOXM1Δ3 or FOXM1Δ6. Diseases and disorders where increasing FOXM1 expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, aberrant cell growth, cell differentiation, aberrant cell migration, tumorigenesis, or cancer including a liver cancer (The et al., 2002, Cancer Res. 62: 4773-80), a breast cancer (Wonsey et al., 2005, Cancer Res. 65 (12): 5181-9), a lung cancer (Kim et al., 2006, Cancer Res. 66 (4): 2153-61), a prostate cancer (Kalin et al., 2006, Cancer Res. 66 (3): 1712-20; a cervical cancer of the uterus (Chan et al., 2008, J. Pathol. 215 (3): 245-52), a colon cancer (Douard et al., 2006, Surgery 139 (5): 665-70), a pancreatic cancer (Wang et al., 2007, Cancer Res. 67 (17): 8293-300), and a brain cancer (Liu et al., 2006, Cancer Res. 66 (7): 3593-602).

In another embodiment, the present invention provides a method of treating a subject afflicted with aberrant cell growth, cell differentiation, aberrant cell migration, tumerigenesis, or cancer. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a FOXM1 pre-mRNA and modulates the splicing of the FOXM1 pre-mRNA to inhibit expression of FOXM1, as described elsewhere herein.

F. Method of Modulating HER3 Receptor Pre-mRNA Splicing

In one embodiment, the present invention provides a method of modulating splicing of HER3 pre-mRNA using a SMO to decrease expression or functionality of HER3 in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a HER3 pre-mRNA and modulates the splicing of the HER3 pre-mRNA. In one aspect, the SMO specifically binds to the complementary sequence and enhances inclusion of intron 3 favoring expression of a truncated, non-functional HER3 protein. In another aspect, the SMO specifically binds to the complementary sequence and enhances exclusion of exon 3 to favor expression of HER3Δ3 to produce a non-functional protein. In still another aspect, the SMO contacts a HER3 pre-mRNA and enhances the exclusion of exon 11 to favor expression of HER3A 11 to produce a non-functional protein. Diseases and disorders where decreasing HER3 expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, aberrant cell growth, cell differentiation, aberrant cell migration, tumerigenesis, cancer, and a metastatic cancer.

In another embodiment, the present invention provides a method of treating a subject afflicted with aberrant cell growth, cell differentiation, aberrant cell migration, tumerigenesis, or a cancer (Baselga et al., 2009, Nat Rev Cancer 9:463-475) including liver (The et al., 2002, Cancer Res. 62: 4773-80) breast, or a metastatic cancer derived from breast (Wonsey et al., 2005, Cancer Res. 65 (12): 5181-9), lung (Kim et al., 2006, Cancer Res. 66 (4): 2153-61), prostate (Kahn et al., 2006, Cancer Res. 66 (3): 1712-20; cervix of uterus (Chan et al., 2008, J. Pathol. 215 (3): 245-52), colon (Douard et al., 2006, Surgery 139 (5): 665-70), pancreas (Wang et al., 2007, Cancer Res. 67 (17): 8293-300), and brain (Liu et al., 2006, Cancer Res. 66 (7): 3593-602). The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a HER3 pre-mRNA and modulates the splicing of the Her3 pre-mRNA to inhibit expression or function of HER3, as described elsewhere herein.

G. Method of Modulating CypD Receptor Pre-mRNA Splicing

In one embodiment, the present invention provides a method of modulating splicing of CypD pre-mRNA using a SMO to inhibit expression or functionality of CypD in a subject. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a CypD pre-mRNA and modulates the splicing of the CypD pre-mRNA to favor expression of CypDΔ1 or CypDΔ3 which exclude exons 1 and 3 respectively. Diseases and disorders where decreasing CypD expression is believed to provide a therapeutic benefit to the subject afflicted with the disease include, but are not limited to, ALS, aberrant cell growth, cell differentiation, aberrant cell migration, tumerigenesis, Hepatitis B infection, and liver cancer.

In another embodiment, the present invention provides a method of treating a subject afflicted with amyotrophic lateral sclerosis (ALS; Sandyk, R., 2006, Int. J. Neurosci. 116: 775-826; Ionov, I. D., 2007, Amyotroph. Lateral Scler. 8:260-265). The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a cyclophilin-D pre-mRNA and modulates the splicing of the CypD pre-mRNA in the subject.

In another embodiment, the present invention provides a method of treating a subject afflicted with aberrant cell growth, cell differentiation, aberrant cell migration, tumerigenesis, hepatitis B infection, and liver cancer. The method comprises administering a SMO of the invention, or a composition comprising a SMO of the invention, to a subject, wherein the SMO contacts a CypD pre-mRNA and modulates the splicing of the CypD pre-mRNA to inhibit expression of CypD, as described elsewhere herein.

Methods of Administration

Examples of methods for introducing oligonucleotides into cells encompass in vivo and ex vivo methods. The oligonucleotides of the invention, i.e. SMOs, are typically administered to a subject or generated in situ such that they hybridize with or bind to pre-mRNA of a specific protein. In one embodiment, the pre-mRNA encodes a 5-HT2CR. In another embodiment, the SMO enhances inclusion of exon 5b during splicing of a 5-HT2CR pre-mRNA. In still another embodiment, the pre-mRNA encodes a glutamate receptor selected from the group consisting of GluR1-4. In yet another embodiment, the SMO modulates the ratio of flip and flop isoforms of any one of, or any combination of, the GluRs. In another embodiment, the pre-mRNA encodes OGA. In yet another embodiment, the pre-mRNA encodes Aph1B. In still another embodiment, the pre-mRNA encodes FOXM1. In still another embodiment, the pre-mRNA encodes HER3. In another embodiment, the pre-mRNA encodes CypD.

The hybridization can be by conventional Watson-Crick base pairing by nucleotide complementarity and/or wobble pairing of U-G or U-A nucleic acids to form a stable duplex. Hybridization can also occur, for example, in the case of an oligonucleotide which binds to DNA duplexes, through specific interactions in the major groove of the double helix.

Conjugation of a SMO to a peptide, liposomes, colloidal polymeric particles as well as other means known in the art may be used to deliver the oligonucleotides to a cell. The method of delivery selected will depend at least on the cells to be treated and the location of the cells and will be known to those skilled in the art. Localization can be achieved by liposomes, having specific markers on the surface for directing the liposome, by having injection directly into the tissue containing the target cells, by having depot associated in spatial proximity with the target cells, specific receptor mediated uptake, or the like.

As described elsewhere herein and in the art, oligonucleotides may be delivered using, e.g., methods involving liposome-mediated uptake, lipid conjugates, polylysine-mediated uptake, nanoparticle-mediated uptake, and receptor-mediated endocytosis, as well as additional non-endocytic modes of delivery, such as microinjection, permeabilization (e.g., streptolysin-O permeabilization, anionic peptide permeabilization), electroporation, and various non-invasive non-endocytic methods of delivery that are known in the art (refer to Dokka and Rojanasakul, Advanced Drug Delivery Reviews 44, 35-49, incorporated in its entirety herein by reference). Methods of delivery may also include:

Cationic Lipids: Naked DNA can be introduced into cells in vivo by complexing the DNA with cationic lipids or encapsulating the DNA in cationic liposomes. Examples of suitable cationic lipid formulations include N-[−1-(2,3-dioleoyloxy) propyl]N,N,N-triethylammonium chloride (DOTMA) and a 1:1 molar ratio of 1,2-dimyristyloxy-propyl-3-dimethylhydroxyethylammonium bromide (DMRIE) and dioleoyl phosphatidylethanolamine (DOPE) (see e.g., Logan, J. J. et al. (1995) Gene Therapy 2:38-49; San, H. et al. (1993) Human Gene Therapy 4:781-788).

Receptor-Mediated DNA Uptake: Naked DNA can also be introduced into cells in vivo by complexing the DNA to a cation, such as polylysine, which is coupled to a ligand for a cell-surface receptor (see for example Wu, G. and Wu, C. H. (1988) J. Biol. Chem. 263:14621; Wilson et al. (1992) J. Biol. Chem. 267:963-967; and U.S. Pat. No. 5,166,320). Binding of the DNA-ligand complex to the receptor facilitates uptake of the DNA by receptor-mediated endocytosis. A DNA-ligand complex linked to adenovirus capsids which naturally disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al. (1991) Proc. Natl. Acad. Sci. USA 88:8850; Cristiano et al. (1993) Proc. Natl. Acad. Sci. USA 90:2122-2126). Carrier mediated gene transfer may also involve the use of lipid-based compounds which are not liposomes. For example, lipofectins and cytofectins are lipid-based positive ions that bind to negatively charged DNA and form a complex that can ferry the DNA across a cell membrane. Another method of carrier mediated gene transfer involves receptor-based endocytosis. In this method, a ligand (specific to a cell surface receptor) is made to form a complex with a gene of interest and then injected into the bloodstream. Target cells that have the cell surface receptor will specifically bind the ligand and transport the ligand-DNA complex into the cell.

Oligonucleotides may be directly introduced into the cell (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism, introduced orally, or may be introduced by bathing a cell or organism in a solution containing the RNA using methods known in the art for introducing nucleic acid (e.g., DNA) into cells in vivo. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are sites where the RNA may be introduced.

The oligonucleotides of the invention can be delivered to a subject by any art-recognized method. For example, peripheral blood injection of the oligonucleotides of the invention can be used to deliver the reagents via diffusive and/or active means. Alternatively, the oligonucleotides of the invention can be modified to promote crossing of the blood-brain-barrier (BBB) to achieve delivery of said reagents to neuronal cells of the central nervous system (CNS). Specific recent advancements in oligonucleotide technology and delivery strategies have broadened the scope of oligonucleotide usage for neuronal disorders (Forte, A., et al. 2005. Curr. Drug Targets 6:21-29; Jaeger, L. B., and W. A. Banks. 2005. Methods Mol. Med. 106:237-251; Vinogradov, S. V., et al. 2004. Bioconjug. Chem. 5:50-60; the preceding are incorporated herein in their entirety by reference).

In certain embodiments, the oligonucleotides of the invention can be delivered by transdermal methods (e.g., via incorporation of the oligonucleotide reagent(s) of the invention into, e.g., emulsions, with such oligonucleotides optionally packaged into liposomes). Such transdermal and emulsion/liposome-mediated methods of delivery are described for delivery of antisense oligonucleotides in the art, e.g., in U.S. Pat. No. 6,965,025, the contents of which are incorporated in their entirety by reference herein.

The oligonucleotides of the invention may also be delivered via an implantable device (e.g., an infusion pump or other such implantable device). Design of such a device is an art-recognized process.

In one embodiment, a SMO is delivered directly into the cerebral spinal fluid (CSF) of a subject. Delivery of a SMO into the CSF of a subject may be accomplished by any means known in the art, including, but not limited to, epidural injection or intrathecal injection via an infusion pump.

In one embodiment, SMOs are conjugated to a peptide to facilitate delivery of the SMO across the blood brain barrier (BBB) following parenteral administration to a subject. The SMO may be either directly conjugated to the peptide or indirectly conjugated to the peptide via a linker molecule such as a poly amino acid linker, or by electrostatic interaction. Peptides useful in delivering SMOs across the BBB include, but are not limited to, peptides derived from the rabies virus glycoprotein (RVG) that specifically bind to the nicotinic acetylcholine receptor (AchR) present on neurons and the vascular endothelium of the BBB thereby allowing transvascular delivery, probably by receptor-mediated transcytosis (Kumar et al., 2007, Nature 448:39-43, encompassed by reference in its entirety); Kunitz domain-derived peptides called angiopeps (Demeule et al., 2008, J. Neurochem. 106:1534-1544; Demeule et al., 2008, J. Pharmacol. Exp. Ther. 324: 1064-1072).

Recombinant methods known in the art can also be used to achieve oligonucleotide reagent-induced modulation of splicing in a target nucleic acid. For example, vectors containing oligonucleotides can be employed to express, e.g., an antisense oligonucleotide to modulate splicing of an exon of a targeted pre-mRNA.

For oligonucleotide reagent-mediated modulation of an RNA in a cell line or whole organism, gene expression may be assayed by use of a reporter or drug resistance gene whose protein product is easily assayed. Such reporter genes include acetohydroxyacid synthase (AHAS), alkaline phosphatase (AP), beta galactosidase (LacZ), beta glucoronidase (GUS), chloramphenicol acetyltransferase (CAT), green fluorescent protein (GFP), horseradish peroxidase (HRP), luciferase (Luc), nopaline synthase (NOS), octopine synthase (OCS), and derivatives thereof. Multiple selectable markers are available that confer resistance to ampicillin, bleomycin, chloramphenicol, gentarnycin, hygromycin, kanamycin, lincomycin, methotrexate, phosphinothricin, puromycin, and tetracyclin. Depending on the assay, quantitation of the amount of gene expression allows one to determine a degree of modulation which is greater than 10%, 33%, 50%, 90%, 95% or 99% as compared to a cell not treated according to the present invention. Lower doses of injected material and longer times after administration of oligonucleotides may result in modulation in a smaller fraction of cells (e.g., at least 10%, 20%, 50%, 75%, 90%, or 95% of targeted cells). Quantitation of gene expression in a cell may show similar amounts of modulation at the level of accumulation of target mRNA or translation of target protein. As an example, the efficiency of modulation may be determined by assessing the amount of gene product in the cell; pre-mRNA or mRNA may be detected with a hybridization probe having a nucleotide sequence outside the region used for the oligonucleotide reagent, or translated polypeptide may be detected with an antibody raised against the polypeptide sequence of that region.

H. Method of Identifying SMOs for Skipping Exons

In general, SMOs function by sterically blocking or weakening interactions between elements of the spliceosomal complex and the pre-mRNA. Factors that influence whether an exon is spliced from its pre-mRNA and included in the mRNA include the strength of the intron-exon splice sites at either end of the exon, and on exonic and intronic regulatory motifs. In general, to facilitate exclusion (skipping) of exons from being included in mRNA of a targeted gene, the SMOs of the invention are designed to be complimentary to sequences encompassing the 5' and/or 3' splice sites and/or ESEs and ISEs and are not-complimentary to (avoid) ESSs and ISSs. Another major determinant of the functionality of SMOs are its thermodynamic properties. The skipping of exons from mRNA transcripts of targeted genes is enhanced by SMOs of the invention using the following set of methods.

(a) Ranking of 5' Splice Site Strength

The relative strength of exonic 5' splice sites is determined by the combination of splice regulatory elements such as ESEs, ESSs, ISEs, and ISSs, as well as how complementary the site is to the binding of the U1 splicing factor. U1 splice site binding is ranked by two criterion: (i) complementarity (Roca, X. et al., 2005, RNA, 11: 683-698) and (ii) thermodynamics of U1 binding to the splice site (Garland, J. A. et al., 2004, Phys Rev E Stat Nonlin Soft Matter Phys, 69: 041903).

(b) Identification ESE/ESS/ISE Motifs

ESE motifs are defined using three prediction tools: ESE Finder (Cartegni, L. et al., 2003, Nucleic Acids Res, 31: 3568-3571), RESCUE-ESE (Fairbrother, W. G. et al., 2002, Science, 297: 1007-1013), and PESX (Zhang, X. H. et al., 2004, Genes Dev, 18: 1241-1250). ESSs are defined using three prediction tools PESX, and a two hexamer data set analysis by FAS-ESS (Wang, Z. et al., 2004, Cell, 119: 831-845). Finally, ISEs are predicted using the ACESCAN2 application (Yeo, G. W. et al., 2005, Proc Natl Acad Sci USA, 102: 2850-2855; Yeo, G. W. et al., 2007, PLoS Genet, 3: e85).

(c) RNA Structure and Oligo Walk

The Oligo Walk function of the publicly available "RNA Structure" program (Mathews, D. H. et al., 2004, Proc Natl Acad Sci USA, 101: 7287-7292) is used to evaluate the predicted open secondary structure of pre-mRNA sequences and the thermodynamic properties of the pre-mRNA. "RNA Structure" also provides analysis of thermodynamic parameters that determine SMO binding strength and efficiency at a given site on the target pre-mRNA.

(1) Duplex ΔG^{o}_{37}: Estimates the Gibbs free energy of the SMO to pre-mRNA binding. More negative values for duplex ΔG^{o}_{37} will improve SMO binding to its target.

(2) Oligo-self ΔG^{o}_{37}: Estimates the free energy of intramolecular SMO structures. More negative values indicate increasing stability of intermolecular structures which may interfere with target binding.

(3) Oligo-oligo ΔG^{o}_{37}: Provides the free energy of intermolecular SMO structures. Negative values indicate more stable SMO-SMO duplexes, thus values of oligo-oligo ΔG^{o}_{37} closer to zero will improve SMO functionality.

(4) T_m: Estimates the melting temperature of SMO-target sequence duplex formation. Higher T_m values will improve SMO binding and specificity.

(5) Break-Target: Provides the energy penalty for breaking of intramolecular RNA target base pairs when oligo is bound. Thus Optimal Break-point ΔG^{o}_{37}:≥0 kcal/mol

(d) BLAST Analysis of Potential Off-Target Hybridization

SMOs are screened using BLASTN analysis for potential hybridization to off-target sites in the human genome. Generally, SMOs with greater than 85% off-target hybridization to any other known pre-mRNA are eliminated from consideration.

(e) Prioritization of SMOs Based on Combined Properties

SMOs are ranked for each of the five thermodynamic criterion with approximate thresholds for criteria 1-3 as in (Matveeva, O. V. et al., 2003, Nucleic Acids Res, 31: 4989-4994) and criterion 4. Criterion 5 is ranked but is not exclusionary. The thermodynamic criterion are combined with the information on splice site strength and splice enhancer motifs to establish candidate SMOs for empirical evaluation of splicing specificity and efficiency.

It is apparent to someone skilled in the art that in most cases SMOs do not meet all criterion and there are necessary compromises made in selecting SMOs for empirical testing. For example a SMO and its target pre-mRNA sequence may be exceptionally favorable from a thermodynamic standpoint, and splice site strength and ESE elements may be strong. However, there may be predicted ESSs that would potentially lower SMO efficiency. The prioritization or weighting of the various factors in are taken into account on a case-by-case basis, when selecting SMOs at a given gene target.

Certain SMOs of the invention are designed to skip 'out of frame' (OOF) exons (coding exon not divisible by 3) that are not alternatively spliced. When constitutive OOF exons are skipped, the codon reading frame is shifted, resulting in an mRNA that encodes inappropriate amino acids followed soon after by a pre-mature stop codon. The protein produced by such OOF exon skipping is non-functional and is degraded. This functions to block protein expression in a cell. Examples exon skipping of OOF exons for the purpose of preventing protein expression in a cell are demonstrated elsewhere herein in the cases of FoxM1, HER3, and CypD.

IV. Pharmaceutical Compositions and Therapies

An SMO of the invention may be administered to a subject in a pharmaceutical composition. As used herein the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions. Pharmaceutical compositions can be prepared as described below.

Depending on the particular target RNA and the dose of oligonucleotide material delivered, this process may modulate function of the target gene. In one embodiment of the instant invention, exon 5b-containing 5-HT2CR protein production is enhanced in a treated cell, cell extract, organism or patient, with an enhancement of exon 5b-containing 5-HT2CR protein levels of at least about 1.1-, 1.2-, 1.5-, 2-, 3-, 4-, 5-, 7-, 10-, 20-, 100-fold and higher values being exemplary. In another embodiment of the invention, flop exon containing GluR protein production is reduced in a treated cell, cell extract, organism, or patient, with a decrease of flip exon GluR protein levels of at least 1.1-, 1.2-, 1.5-, 2-, 3-, 4-, 5-, 7-, 10-, 20-, 100-fold and higher values being exemplary. Enhancement of gene expression refers to the presence (or observable increase) in the level of protein and/or mRNA product from a target RNA. Specificity refers to the ability to act on the target RNA without manifest effects on other genes of the cell. The consequences of modulation of the target RNA can be confirmed by examination of the outward properties of the cell or organism (as presented below in the examples) or by biochemical techniques such as RNA solution hybridization, nuclease protection, Northern hybridization, reverse transcription, gene expression monitoring with a microarray, antibody binding, enzyme linked immunosorbent assay (ELISA), Western blotting, radioimmunoassay (RIA), other immunoassays, and fluorescence activated cell analysis (FACS).

The oligonucleotide, i.e. the SMO, may be introduced in an amount which allows delivery of at least one copy per cell. Higher doses (e.g., at least 5, 10, 100, 500 or 1000 copies per cell) of material may yield more effective modulation; lower doses may also be useful for specific applications.

Although the description of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for ethical administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, mammals including commercially relevant mammals such as non-human primates, cattle, pigs, horses, sheep, cats, and dogs.

Pharmaceutical compositions that are useful in the methods of the invention may be prepared, packaged, or sold in formulations suitable for ophthalmic, oral, parenteral, intranasal, buccal, or another route of administration. Other contemplated formulations include projected nanoparticles, liposomal preparations, resealed erythrocytes containing the active ingredient, and immunologically-based formulations.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in bulk, as a single unit dose, or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, intraocular, intravitreal, subcutaneous, intraperitoneal, intramuscular, intrasternal injection, intratumoral, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e. powder or granular) form for reconstitution with a suitable vehicle (e.g. sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer systems. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or aerosolized formulations, when dispersed, preferably have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

As used herein, "additional ingredients" include, but are not limited to, one or more of the following: excipients; surface active agents; dispersing agents; inert diluents; granulating and disintegrating agents; binding agents; lubricating agents; sweetening agents; flavoring agents; coloring agents; preservatives; physiologically degradable compositions such as gelatin; aqueous vehicles and solvents; oily vehicles and solvents; suspending agents; dispersing or wetting agents; emulsifying agents, demulcents; buffers; salts; thickening agents; fillers; emulsifying agents; antioxidants; antibiotics; antifungal agents; stabilizing agents; and pharmaceutically acceptable polymeric or hydrophobic materials. Other "additional ingredients" which may be included in the pharmaceutical compositions of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (1985, Genaro, ed., Mack Publishing Co., Easton, Pa.), which is incorporated herein by reference.

The therapeutic and prophylactic methods of the invention thus encompass the use of pharmaceutical compositions comprising a splice modifying oligonucleotide of the invention to practice the methods of the invention. The precise dosage administered will vary depending upon any number of factors, including but not limited to, the type of animal and type of disease state being treated, the age of the animal and the route of administration.

The compound may be administered to an animal as frequently as several times daily, or it may be administered less frequently, such as once a day, once a week, once every two weeks, once a month, or even less frequently, such as once every several months or even once a year or less. The frequency of the dose will be readily apparent to the skilled artisan and will depend upon any number of factors, such as, but not limited to, the type and severity of the disease being treated, the type and age of the animal, etc. The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit.

III. Kits

Kits for practicing the methods of the invention are further provided. By "kit" is intended any manufacture (e.g., a package or a container) comprising at least one reagent, e.g., at least one SMO for specifically enhancing inclusion of exon 5b in the 5-HT2C receptor for the treatment of Prader-Willi Syndrome, a 5-HT2CR splicing deficit, hyperphagia resulting from a 5-HT2CR splicing deficit, and/or symptoms of obsessive-compulsive disorder resulting from a 5-HT2CR splicing deficit. In one embodiment, the kit includes at least one SMO directed to a GluR for the treatment of epilepsy, a seizure disorder, or ALS. In still another embodiment, the kit includes at least one SMO directed to Aph1B for the treatment of Alzheimer's Disease. In yet another embodiment, the kit of the invention includes at least one SMO directed to OGA for the treatment of Alzheimer's Disease. In a still further embodiment, the kit includes at least one SMO directed to FOXM1 for the treatment of a carcinoma. In still another embodiment, the kit includes at least one SMO directed to HER3 for the treatment of breast cancer. In yet another embodiment, the kit includes at least one SMO directed to CypD for the treatment of ALS or liver cancer. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention. Additionally, the kits may contain a package insert describing the kit and including instructional material for its use.

Positive, negative, and/or comparator controls may be included in the kits to validate the activity and correct usage of reagents employed in accordance with the invention. Controls may include samples, such as tissue sections, cells fixed on glass slides, etc., known to be either positive or negative for the presence of the biomarker of interest. The design and use of controls is standard and well within the routine capabilities of those of ordinary skill in the art.

EXPERIMENTAL EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

The materials and methods employed in the experiments and the results of the experiments presented in these Examples are now described.

Experimental Example 1

Design and Validation of Antisense Oligonucleotides to Increase Inclusion of Exon 5b in the 5-HT2C Receptor

The snoRNA HBII-52 promotes inclusion of exon Vb in the 5-HT2C receptor by blocking a splice silencing element in the consensus region of 5-HT2C. Thus an oligonucleotide identical to the consensus sequence of MBII-52 (the mouse homolog) was designed to block the silencing site on 5-HT2C. The first oligonucleotide was designed using a phosphorothioate linkages between nucleotides and O-methyl substitutions on the 2' ribose and is identical to the MBII-52 complementary box as follows: AUGCUCAAUAGGAUUACG (SEQ ID NO. 1).

Smaller SMOs may permit more specific targeting of inhibitory elements in 5-HT2C. Therefore, a series of SMOs of varying lengths were designed using an “antisense walk strategy” that has been recently used to successfully target inhibitory regions in the SMN gene to correct splicing (Hua et al., 2007, Public Library of Science Biol. 5:e73). The SMO was “walked” base by base beginning with the 5'-most nucleotide (nt) aligned at the +3 nt position relative to the consensus sequence on 5-HT2CR pre-mRNA and ending with the 3'-most nt of the oligomer at the −3 nt position of the consensus sequence. This strategy resulted in SMOs that incrementally span the consensus region (Table 1 through Table 15). To ensure proper hybridization efficiency, these smaller SMOs may be composed of an appropriate number of locked nucleic acid (LNA) residues substituted for 2'-O-methyl nucleotides.

To validate these SMOs, the SMOs are transfected into undifferentiated NG108-15 cells that have previously been demonstrated to express both 5-HT2CR splice isoforms (5a and 5b), the ratio of which can be detectably altered by differentiation (Tohda et al., 2002, Jpn. J. Pharmacol. 90:138-144; Sukma et al., 2003, J. Pharmacol. Sci. 92:433-436; Tohda et al., 2004, J. Pharmacol. Sci. 96:164-169). Cells are harvested 48 hours post-transfection. Real-time PCR is used to quantify amounts of 5-HT2CR containing exon 5a and 5b. An SMO that mimics the effect of MBII-52 increases the ratio of 5b to 5a transcripts. Western blotting is also performed using a rabbit polyclonal antibody (Abcam) to quantify upregulation of full-length 5-HT2CR protein.

Experimental Example 2

Phenotypic Improvement in Spinal Muscular Atrophy (SMA) Mice by SMO-Mediated Induction of SMN Expression

Spinal Muscular Atrophy (SMA) is caused by mutations in the SMN I gene, which encodes a protein called “survival of motor neuron” or SMN, a ubiquitous protein involved in RNA processing (Gubitz et al., 2004, Exp. Cell Res. 296:51-56; Monani, 2005, Neuron 48:885-896). The potential of the SMO developed by the Singh group (Singh et al., 2006, Mol. Cell. Biol. 26:1333-1346) to induce SMN expression and improve functional performance in vivo in the SMNΔ$7^{+/+}$; SMN$2^{+/+}$; Smn$^{-/-}$ mice with severe type 1 SMA phenotype was recently examined (Le et al., 2005, Hum. Mol. Genet. 14:845-857). First, to assess SMO distribution throughout the CNS, FAM-SMO was delivered intracerebroventricular (ICV) and fluorescent label was imaged in cryosections of brains and spinal cords (FIG. 1A-C). SMO was found to be broadly but not uniformly distributed throughout the brain and spinal cord regions. These data were in accordance with previous studies showing very effective CNS biodistribution of SMOs of similar chemistry after both intrathecal and ICV delivery (Smith et al., 2006, J. Clin. Invest. 116:2290-2296).

When SMA mice were given periodic intracerebroventricular injections of SMO they showed greatly enhanced SMN expression at post-natal day 12 in both brain and spinal cord, reaching 35-50% of the levels in wild-type littermates (FIG. 1D-E). On average, SMN expression in the hippocampus region of SMA mice injected with SMO was 34.4±1.8%, which was significantly greater than the 13.8±1.0% in uninjected SMA controls (2.5-fold increase; $P<0.001$). Importantly, the high level of SMN expression in brain and spinal cord of SMA mice after ICV injection of SMO alone was accompanied by a significant improvement in body weight during post-natal development compared with un-treated SMA mice (FIG. 1E). These data represent the highest level of SMN expression reported to date in CNS of SMA mice. These data document that SMOs are broadly distributed and biologically active in CNS after ICV delivery.

Experimental Example 3

Determination of the Ability of Optimal SMO to Increase Inclusion of 5-HT2CR Vb In Vivo

SMOs are injected ICV into brains of normal mice (C57bl/6J) for 1 week via a cannula. Optimal dose and dosing regimens are around 2 μg/day for 1 week, but can be optimized by the skilled artisan. Mouse brains are harvested one day after final injection, sub-regions are dissected out (hippocampus, cortex, hypothalamus) and trizol-extracted. Real time (RT) PCR is performed using primers previously shown to be able to distinguish Va and Vb splice variants (Kishore and Stamm, 2006, Science 311:230-232). Since both splice variants are present and detectable in normal mouse brain (Canton et al., 1996, Mol. Pharm. 50:799-807), injection of SMOs will lead to a detectable increase in the ratio of exon 5b to exon 5a-containing isoforms. Western blotting using a rabbit polyclonal antibody (Abeam) is used to determine whether expression of full-length 5-HT2CR protein has been up-regulated.

Experimental Example 4

Examination of Functional Consequence of Modulating 5-HT2CR Splicing Using Electrophysiological Techniques in Hippocampal Slices

By increasing inclusion of exon 5b in 5-HT2CR, the expression of functional receptor is also increased. Both 5a and 5b-containing transcripts are abundantly present in hippocampus (Canton et al., 1996, Mol. Pharmacol. 50:799-807), and it has been demonstrated elsewhere herein that SMO injected ICV can notably increase SMN levels in this brain region. Therefore initial electrophysiological assessment is in hippocampal slices. Activation of 5-HT2CR leads to an increase in intrinsic neuronal excitability and glutamate-mediated excitatory postsynaptic current (EPSC) amplitudes in hippocampal CA1 pyramidal neurons (Beck, 1992, Synapse 10:334-340). These studies are done using the selective 5-HT2CR agonist Ro 60-175 (100 nM). The hippocampal slice preparation and whole-cell patch clamping techniques are used to record from CA1 pyramidal neurons. Intrinsic excitability is measured using current-clamp protocols to measure firing properties of neurons in response to voltage steps. EPSC measurements are done using voltage-clamp, and measuring synaptic responses to stimulation of Schaffer collateral input. These techniques are described in (Tallent and Siggins, 1999, J. Neurophysiol. 81:1626-1635; Tallent et al., 2001, J. Neurosci. 21:6940-6948), incorporated herein by reference, in their entirety. An enhancement in the ability of Ro 60-175 to increase excitability and EPSC amplitude after ICV injection of an optimal SMO is due to increases in the expression of functional receptor in CA 1 neurons.

Experimental Example 5

GluR Subunit Selection and SMO Design

The pre-mRNA splicing pattern of GluR subunits of the AMPA receptor is shown in FIG. **2**. GluRs typically contain either of two mutually-exclusive alternative exons, flip or flop. Thus, the flip/flop exons constitute classical cassette exons, as opposed to constitutive exons which are always retained in mRNA transcripts.

2' OMe SMO that target exonic splice enhancers (ESEs) and splice site of the flip exons of GluRs are developed that facilitate specific skipping of flip exons of GluR pre-mRNAs by masking exon recognition by the spliceosome proteins. When an exon does not get spliced, it is removed (skipped) along with the introns on either side of it. The specific GluR flip subunits to be targeted as potential therapeutic agents for treating ALS include GluR 3, GluR3+GluR4, GluR1, GluR1+GluR3, and GluR1+GluR2+GluR3+GluR4. Because of the nature of conservation/divergence in ESEs and splice junctions of the flip exons of GluRs, it is possible to selectively target any individual GluR for flip exon skipping, but it is not possible to target all possible combinations. For example it may be difficult to target ESEs of both GluR1 and GluR3 in tandem without also impacting an ESE of GluR2. It would likely be even more difficult to target only the GluRs that provide Ca^{2+} permeability to the AMPA receptor (GluR1, GluR3, and GluR4), without also impacting GluR2. Given these constraints, GluR pre-mRNA targets for treating ALS would be as follows:

(a) Ranking of 5' Splice Site Strength

The relative strength of exonic 5' splice sites is determined by the combination of splice regulatory elements such as ESEs, ESSs, ISEs, and ISSs, as well as how complementary the site is to the binding of the U1 splicing factor. U1 splice site binding is ranked by two criterion: (i) complementarity (Roca, X. et al., 2005, RNA, 11: 683-698) and (ii) thermodynamics of U1 binding to the splice site (Garland, J. A. et al., 2004, Phys Rev E Stat Nonlin Soft Matter Phys, 69: 041903).

(b) Identification ESE/ESS/ISE Motifs

ESE motifs are defined using three prediction tools: ESE Finder (Cartegni, L. et al., 2003, Nucleic Acids Res, 31: 3568-3571), RESCUE-ESE (Fairbrother, W. G. et al., 2002, Science, 297: 1007-1013), and PESX (Zhang, X. H. et al., 2004, Genes Dev, 18: 1241-1250). ESSs are defined using three prediction tools PESX, and a two hexamer data set analysis by FAS-ESS (Wang, Z. et al., 2004, Cell, 119: 831-845). Finally, ISEs are predicted using the ACESCAN2 application (Yeo, G. W. et al., 2005, Proc Natl Acad Sci USA, 102: 2850-2855; Yeo, G. W. et al., 2007, PLoS Genet, 3: e85).

(c) RNA Structure and Oligo Walk

The Oligo Walk function of the publicly available "RNA Structure" program (Mathews, D. H. et al., 2004, Proc Natl Acad Sci USA, 101: 7287-7292) is used to evaluate the predicted open secondary structure of pre-mRNA sequences and the thermodynamic properties of the pre-mRNA. "RNA Structure" also provides analysis of thermodynamic parameters that determine SMO binding strength and efficiency at a given site on the target pre-mRNA.

(1) Duplex ΔG^{o}_{37}: Estimates the Gibbs free energy of the SMO to pre-mRNA binding. More negative values for duplex ΔG^{o}_{37} will improve SMO binding to its target.

(2) Oligo-self ΔG^{o}_{37}: Estimates the free energy of intramolecular SMO structures. More negative values indicate increasing stability of intermolecular structures which may interfere with target binding.

(3) Oligo-oligo ΔG^{o}_{37}: Provides the free energy of intermolecular SMO structures. Negative values indicate more stable SMO-SMO duplexes, thus values of oligo-oligo ΔG^{o}_{37} closer to zero will improve SMO functionality.

(4) T_m: Estimates the melting temperature of SMO-target sequence duplex formation. Higher T_m values will improve SMO binding and specificity.

(5) Break-Target: Provides the energy penalty for breaking of intramolecular RNA target base pairs when oligo is bound. Thus Optimal Break-point ΔG^{o}_{37}: ≥ 0 kcal/mol

(d) BLAST Analysis of Potential Off-Target Hybridization

SMOs are screened using BLASTN analysis for potential hybridization to off-target sites in the human genome. Generally, SMOs with greater than 85% off-target hybridization to any other known pre-mRNA are eliminated from consideration.

(e) Prioritization of SMOs Based on Combined Properties

SMOs are ranked for each of the five thermodynamic criterion with approximate thresholds for criteria 1-3 as in (Matveeva, O. V. et al., 2003, Nucleic Acids Res, 31: 4989-4994) and criterion 4. Criterion 5 is ranked but is not exclusionary. The thermodynamic criterion are combined with the information on splice site strength and splice enhancer motifs to establish candidate SMOs for empirical evaluation of splicing specificity and efficiency.

Experimental Example 6

Measure Relative Efficacy of SMOs Using Mouse Line Endogenously Expressing all Four GluR5

For analysis of SMO effectiveness, SMOs designed against the targets listed in Table 2 through Table 7 are transfected into NSC-34 cells which are mouse neuroblastoma-spinal neuron hybrids that endogenously express all four mouse GluR5 (Eggett et al., 2000, J. Neurochem. 74:1895-1902; Rembach et al., 2004, J. Neurosci. Res. 77:573-582). The NSC-34 cell line is used widely as a culture model system for the study of motor neurons (Cashman et al., 1992, Dev. Dyn. 194:209-221; Eggett et al., 2000, J. Neurochem. 74:1895-1902). NSC-34 cells were found to express low levels of GluR2 compared to GluR1, 3, and 4. This is consistent with published reports that motor neurons are deficient in GluR2, thus rendering these cells vulnerable to calcium-mediated damage and excitotoxicity (Bar-Peled et al., 1999, Neuroreport 10:855-859; Heath et al., 2002, Neuroreport 13:1753-1757; Van et al., 2002, J. Neurophysiol. 88:1279-1287; Williams et al., 1997, Ann. Neurol. 42:200-207). NSC-34 cells have also been shown to efficiently uptake SMOs in culture (Rembach et al., 2004, J. Neurosci. Res. 77:573-582). Briefly, SMOs are complexed with lipofectamine and applied to NSC-34 cells (100 SMO) in reduced serum medium for 4-6 hours (Cashman et al., 1992, Dev. Dyn. 194:209-221; Eggett et al., 2000, J. Neurochem. 74:1895-1902). Medium is replaced and cells are grown for an additional 24-48 hours in serum-containing medium and harvested. Cells are lysed, total RNA extracted (Trizol), and cDNA generated a reverse transcriptase (MultiScribe) using dNTPs and random hexamers. The level of both flip- and flop-containing mRNA transcripts is determined for each of the GluRs using real-time PCR (TaqMan PCR system).

Next, SMOs that show the greatest decrease in the targeted flip isoforms are evaluated more extensively. The dose-response of lead SMOs are analyzed by treating cells with concentrations ranging from 0-100 μM. Westerns blots are used to quantify GluR protein levels with antibodies to GluR1 (1:100, AB5849; Chemicon), GluR2 (1:100, AB1768; Chemicon), GluR3 (1:1,500; (Gahring et al., 1998, Autoimmunity 28:243-248)), and GluR4 (1:100, AB1508; Chemicon). Toxicity is quantified by documenting morphology of nuclei (DAPI), a known hallmark of cell damage.

An iterative process of SMO evaluation and optimization is used where the efficacy of the 2 top-ranked SMOs is performed, and these data used to make the next SMO choices in a strategic manner. For example if a SMO shows a significant but incomplete reduction in flip isoform expression, bases are added or subtracted from either end to further improve efficacy.

Experimental Example 7

Determine Changes in Electrophysiological Properties of AMPA Currents after Treatment with Lead SMOs

The SMOs that produce the most efficacious skipping of flip exons are transfected into NSC-34 cells and AMPA-receptor mediated currents are studied using whole cell patch clamp. Changes in flip/flop ratios of GluRs change properties of AMPA receptor-mediated currents. Increases in the flop to flip ratio result in the following changes in AMPA receptor currents: (i) An increase in desensitization kinetics (Sommer et al., 1990, Science 249:1580-1585). (ii) A decrease in the sensitivity to cyclothiazide (Johansen et al., 1995, Mol. Pharm. 48:946-955; Partin et al., 1994, Neuron 14:833-843) and an increase in the sensitivity to PEPA (Sekiguchi et al., 1998, Br. J. Pharmacol. 123:1294-1303). (iii) A decrease in sensitivity for glutamate (Partin et al., 1995, Neuron 14:833-843; Sommer et al., 1990, Science 249:1580-1585).

NSC-34 cells have also been shown to efficiently uptake SMOs in culture (Rembach et al., 2004, J. Neurosci. Res. 77:573-582). Briefly, SMOs are complexed with lipofectamine and applied to NSC-34 cells (100 μM SMO) in reduced serum medium for 4-6 hours (to induce differentiation (Eggett et al., 2000, J. Neurochem. 74:1895-1902; Rembach et al., 2004, J. Neurosci. Res. 77:573-582). Medium is replaced and cells grown for an additional 24-48 hours in serum-containing medium and harvested. Cells are lysed, total RNA extracted (Trizol), and cDNA generated with a reverse transcriptase (MultiScribe) using dNTPs and random hexamers. The level of both flip- and flop-containing mRNA transcripts is determined using real-time PCR using the TaqMan PCR system.

The whole-cell patch clamp method is used to record from treated and untreated cells using a perfusion chamber. Cells are voltage-clamped at −70 mV and 1 mM or 10 mM glutamate or AMPA is applied using a rapid superfusion system. AP5 is used to block NMDA receptors. To evaluate desensitization kinetics, 100 millisecond (ms) pulses of glutamate (Gardner et al., 2001, J. Neurosci. 21:7428-7437) are used. Desensitization kinetics are measured by fitting the decay of the AMPA current with single and double exponentials using Clampfit software (Molecular Devices).

To determine cyclothiazide sensitivity, this drug (1-100 μM) is co-applied with 10 mM glutamate for 3 sec. For PEPA experiments, 10 mM glutamate and 1-1000 μM PEPA are co-applied for 1 sec. Dose-response curves are generated and desensitization kinetics determined as described above. Difference in sensitivity to PEPA is greatest for GluR3 flip vs. flop, so this drug may be especially useful in determining an increase in GluR3 flop (Sekiguchi et al., 1998, Br. J. Pharmacol. 123:1294-1303).

Glutamate sensitivity is determined by applying different concentrations of glutamate (50 to 5000 μM) and generating dose-response curves of maximal current response. Since flip isoforms have a higher relative sensitivity to glutamate vs. kainate, the responsiveness of individual cells to 300 μM glutamate vs. 300 μM kainite is also assessed (Partin et al., 1995, Neuron 14:833-843; Sommer et al., 1990, Science 249:1580-1585).

Experimental Example 8

In Vivo Application of SMOs

A cannula is implanted into the third ventricle (coordinates: midline, 0.25 mm posterior to the bregma and 3 mm below the pial surface). Injection into the third ventricle (ICV) gives good access to the hippocampus (Chauhan et al., 2001, J. Neurosci. Res. 66:231-235). Forty eight hours following surgery, delivery of SMO ICV is begun daily for 1 week. SMOs are dissolved in sterile saline at 1 μg/μL. Optimal dose and dosing regimens can be determined by the skilled artisan, but based on previous experience, is around 2 μg/day for 1 week. Mouse brains are harvested one day after final injection, hippocampus dissected out and trizol-extracted. Real time (RT) PCR is performed using primers previously shown to specifically amplify flip and flop splice variants (Seifert et al., 2003, Mol. Cell. Neurosci. 22:248-258; Gomes et al., 2007, Mol. Cell. Neurosci. 37(2): 323-334). Significant changes in splicing are confirmed using Western blotting to determine if there are detectable changes in GluR1 protein levels.

ICV injection of the SMOs (N=5) that target GluR3-flip and GluR1-flip were made in neonatal FVB mice on postnatal days 1, 3, and 5. Control injections of saline were also made (N=4). ICV injection of the SMOs that target GluR3-flip and GluR1-flip produce potent and specific reduction in targeted transcript expression in brain tissue harvested 24 hours after the final administration of SMO (FIG. **3**). Flip and flop transcript levels of all GluRs were measured using real-time PCR. Both the GluR3 and the GluR1SMOs produced nearly complete reduction in targeted transcription expression with no significant effect on other GluR isoforms. Decreasing flip in principle neurons and glia is protective against seizures (Seifert et al., 2004, J. Neurosci. 24:1996-2003; Ge et al., 2006, Science 312:1533-1537).

ICV injections of the SMOs that target all four GluR flip isoforms neonatal FVB mice on postnatal days 1, 3, and 5 produce potent reduction in GluR1, GluR2, and GluR3 flip transcript expression in brain tissue harvested 24 hours after the final administration of SMO (FIG. **4**). A concomitant increase in flop transcripts was also observed.

Experimental Example 9

Efficacy of SMO in Modulating Seizure Activity in Mice

Neonatal mice were administered ICV injections of GluR1SMO on postnatal day 1, 3, and 5 and tested for seizure activity on postnatal day 10. Control ICV injections of saline were also done. Seizures were induced via an intraperitoneal injection of kainic acid and the stage of seizure was evaluate from the least severe (stage 3) to status epilepticus (stage 6). GluR1SMO administration significantly reduces the percent of mice entering stage 4, stage 5, and stage 6 seizures (FIG. **5**).

Experimental Example 10

Using SMOs to Target HER3 and Treat Breast Cancer

SMOs as described elsewhere herein are developed which potently and specifically reduce HER3 expression in a cell, reduce tumorigenesis of HER2 overexpressing breast cancer cells (HOBCs) in vitro, and block metastasis in vivo. The SMOs specifically modulate HER3 pre-mRNA splicing, resulting in downregulation of functional full-length HER3. All SMOs are synthesized using of 2'MOE chemistry and designed to target identified naturally occurring non-functional alternative splice variants of HER3, as well as novel isoforms. HER3-specific SMOs are evaluated for efficacy by transfecting HOBC lines (including SKBR3, BT474, and MDA-MB-453 cell lines). Changes in HER3 expression in cells transfected with SMOs are evaluated using real-time PCR and Western blot analysis to determine the level of HER3 expression at the nucleic acid and protein level. The effects of SMOs on activation of Akt pathway in breast cancer cells using phosphospecific antibodies is also done. Cell lines are also transfected with scrambled SMOs as a negative controls.

SMOs are evaluated in HBOCs (primarily SKBR3 cells) by measuring several indices of oncogenic activity including effects on: (i) growth in soft agar, (ii) survival from matrix detachment, and (iii) invasion using transwell invasion assays.

Liver is a primary site of metastasis of HOBCs. SMOs localize most specifically to liver after IV and IP delivery (Yu et al., 2009, Biochem. Pharmacol. 77:910-919). The efficacy of SMOs directed against HER3 in blocking breast cancer cell metastasis in liver is evaluated as follows. SKBR3 cells (1×10^6), stably transformed to express luciferase reporter, are administered through the tail vein of scid mice (N=10), immediately followed by IV injection of an HER3 targeted SMO. SMOs are injected weekly (IV) for about 6 weeks. The determination of the optimal interval for administering a SMO is well without routine experimental optimization in the art. Metastasis in liver and other organs is visualized with the quantitative IVIS Lumina Imaging System. Livers are then removed and analyzed for indices of macro and micrometastasis. HER3 expression is measured using immunohistochemistry. Mice (N=10) injected with SKBR3 cells and scrambled SMOs are controls.

Experimental Example 11

Using SMOs to Target OGA to Reduce Tau Hyperphosphorylation in Treat Alzheimer's Disease

SMOs which target splicing of both human and mouse OGA pre-mRNA to generate splice isoforms with dominant negative properties and reduced catalytic efficiency have been developed according to the methods described elsewhere herein. Exemplary SMOs targeted to produce the OGA10t and OGAΔ8 isoforms are depicted in Table 7 and Table 8.

SMOs are evaluated for their effect on O-GlcNAc levels by western blot of total protein in a cell using anti-O-GlcNAc antibody CTD110.6 (Dorfmueller et al., 2009, Biochem. J. 420:221-227). OGA splice isoforms with lowered catalytic activity result in increases of O-GlcNAcylation of proteins, since OGA will continue to attach O-GlcNAc residues on nuclear and cytoplasmic targets more rapidly than they can be removed (Yuzwa et al., 2008, Nat. Chem. Biol. 4:483-490).

SMOs are specifically delivered to the CNS by ICV injection to avoid off target peripheral effects. SMOs are delivered using short term continuous infusion of a pharmaceutical composition comprising an SMO by a stereotaxically implanted cannulae in the lateral brain ventricle and connected to a sub-cutaneously implanted osmotic pump (Alzet). Normal mice are administered either saline or a dose of SMO ranging from 1-10 μg of SMO daily for 3 weeks (Smith et al., 2006, J. Clin. Invest. 116:2290-2296). During the 3 weeks of SMO infusion, mice are evaluated weekly for declarative and spatial memory, and motor deficits by Morris water maze, novel object recognition, and rotarod testing.

Following the period of SMO administration, mice are euthanized and brain tissue (including cortex and hippocampus) extracted for testing. Real-time PCR performed on brain sections to determine transcript levels of the desired OGA10t or OGAΔ8 alternative splice isoforms. Brain tissue from saline and SMO dosed mice is also be evaluated by western blot for global increases in O-GlcNAc levels.

Triple Transgenic Alzheimer's (3× Tg) mice are administered SMOs at a dose which provides optimal effects on increasing O-GlcNAc levels. The 3× Tg mice are transgenic for $PS1_{M146V}$, APP_{Swe}, and tau_{p301L} mutations and demonstrate earlier onset of cognitive and synaptic dysfunction as compared to other AD mouse models. Onset of obvious pathology in 3×-Tg mice occurs at 6 months of age with the presence of synaptic and cognitive deficits and at 12 months the presence of tau immunoreactivity can be detected (Oddo et al., 2003, Neuron 39:409-421; Pietropaolo et al., 2008, Behav. Neurosci. 122:733-747). Thus, SMO treatment from 11-12 months of age when tau should be in a hyperphosphorylated state in addition to the presence of synaptic and cognitive deficits due to Aβ deposition, allows for short term evaluation of the effects of increased O-GlcNAc levels on overall cognitive symptoms as well as tau phosphorylation state.

Eleven month old 3× Tg mice are treated with saline or an SMO using the ICV infusion method described elsewhere for 3 weeks. During infusion period, mice are evaluated weekly for cognitive, memory, and motor deficits by Morris water maze, novel object recognition, and rotarod testing. These mice are also tested for effect on total brain O-GlcNAc levels. The mice are euthanized after 3 weeks of infusion (at ~12 months of age). Brain tissue samples from SMO treated 3× Tg mice is evaluated at the end of the dosing period for total O-GlcNAcylation levels by western blot as compared to saline controls.

The effect of SMO that target OGA pre-mRNA on tau phosphorylation is evaluated using the same protocol described above. Samples are taken from the cortex and hippocampus and evaluated for total tau phosphorylation using tau epitope 5 antibody, modification-state specific antibodies (pSer422, pSer262, pSer396, and pThr231), and tau epitope 1 antibody directed against non-phosphorylated residues at Ser198, Ser199 and Ser202. By using this panel of antibodies, changes in phosphorylation state of all the relevant phosphorylation sites is evaluated by Western blot (Yuzwa et al., 2008, Nat. Chem. Biol. 4:483-490). Prevention of tau phosphorylation at these residues by altering splicing of OGA pre-mRNA will block progression of tau pathology in AD.

Experimental Example 12

Using SMOs to target Aph1B to Treat Alzheimer's Disease

A "triple-transgenic" mouse model, 3×-tg AD mice, expresses mutant APP, PSN1 (presenilin), and tau transgenes. These mice have cognitive and synaptic dysfunction similar to those in other AD mice, but with earlier onset (Oddo et al., 2003, Neuron 39:409-421). Specifically, the 3×-tg Ad mice show significant memory deficits when tested using the Morris Water Maze paradigm as early as 120 days of age.

SMOs that target Aph1B, as exemplified by oligonucleotides listed in Table 9, are used to modulate splicing Aph1B pre-mRNA. An SMO that targets Aph1B pre-mRNA is infused ICV for about a 3 week period beginning at 100 days of age. This provides adequate time for the SMO to exert its effect on Aph1B pre-mRNA splicing. In addition, mice are ~4 months of age at the end of the infusion period when they are evaluated for changes in cognitive performance.

For continuous delivery of SMO to the CSF, mice are cannulated stereotaxically into the lateral ventricle, with the cannula tubing already connected to a sub-cutaneously implanted Alzet mini pump pre-loaded with a pharmaceutical composition comprising a SMO. The pharmaceutical composition comprising the SMO is equilibrated for 2 days in sterile saline at 37° C. In this system, the cannulae, tubing, and pump is surgically implanted beneath the skin. The model pump used in these experiments delivers its contents at a constant rate of 4 μL per day and holds enough volume (100 μL) to last about 25 days. We use dosing rates of 1 to 10 μg SMO per day in mice.

Examples of SMOs that specifically skip exon 4 of the Aph1B pre-mRNA are provided in Table 9. These SMOs were developed according to the following rational: Aph1B naturally expresses a non-functional alternative splice variant missing exon 4 (Saito et al., 2005, Biochem. Biophys. Res. Comm. 330:1068-1072). Alternatively spliced exons are known to be more readily modulated by oligomers than constitutive exons. Second, exon 4 of Aph1B contains a conserved GXXXG motif, critical for the assembly and activity of the γ-secretase complex (Lee et al., J. Biol. Chem. 279: 4144-4152). Thus, Aph1B protein missing exon 4 is non-functional and unstable (Saito et al., 2005, Biochem. Biophys. Res. Comm. 330:1068-1072).

An SMO is transfected into neuroblastoma SY5Y cells that express γ-secretase. SMOs are complexed with lipofectamine and applied to SY5Y cells at a concentration of 100 μM SMO for 4 hours. The bathing medium is replaced and cells are maintained in culture for an additional 24 hours before they are and harvested. RNA is extracted using standard techniques known in the art, and cDNA generated with superscript RT using oligo-dT and random hexamers. The level of Aph1B mRNA transcripts with and without exon 4 is determined using Real-time PCR. The dose-response of lead SMOs will is analyzed using Westerns blots to quantify Aph1B protein expression in transfected cells. Toxicity is also quantified by documenting morphology of nuclei and using DAPI staining, a known hallmark of cell damage (Martin et al., 2005, Cytometry Part A 67A:45-52).

At the end of the infusion period, mice are evaluated for changes in cognitive performance using the Morris Water Maze test with training beginning at the end of the 3 week drug infusion period. The Morris Water Maze comprises a 25 gallon tub 71 cm in diameter and 33 cm high containing water maintained at 23° C. A platform 6 cm in diameter is placed in the center of one quadrant. The mice have 2 blocks of 4 visible platform trials where they are given 60 seconds to reach the platform, with a 5 min inter-trial interval (Varvel et al., 2005, Psychopharmacol. (Berl) 179:863-872). Location of the platform is changed semi-randomly between trials. Mice are videotaped and latency to reach the platform is recorded. The following day the mice begin hidden platform training where the platform is submerged in opaque water. 2 blocks of 4 trials each (5 minute inter-trial interval) are run each day for 4 days, with 1 hour between blocks. A trial consists of semi-randomly placing the mouse in one of three quadrants without the platform and giving the mouse 60 seconds to locate the platform. The platform remains in the same location for the 4 days of hidden platform training.

Probe tests are run 24 and 72 hours after the final day of training. The platform is removed from the tub and the mice are semirandomly placed in one of the four quadrants and allowed to swim for 30 seconds. After the 24 hour probe the platform is placed back in the same location and the mouse allowed to find it, to minimize extinction. The percent time spent in each quadrant is recorded. A one way ANOVA is run (Statistica) to determine significance in probe trials. A repeated measures ANOVA is used to determine differences in latencies to reach the platform during training, with a post-hoc Tukey's test to determine where the significant differences occur.

Following the final behavioral test, mice are euthanized and brains rapidly removed. The left and right hippocampus and cortex are quickly excised. To alleviate biases due to potential differences between the left and right hemisphere tissues, each assay is performed on an equal number of left and right hemisphere tissues. RNA is immediately extracted from half of the hippocampus and cortex tissues, and cDNA prepared according to standard techniques known in the art. The remaining tissue is immediately processed for protein extraction and the preparation of a soluble fraction and a membrane fraction. Both soluble and membrane fraction preparations will be treated as described below.

Transcript and protein levels of Aph1B in the hippocampus and cortex are measured for all groups. Transcript levels of Aph1B will be measured by Real-time PCR, using custom primer-probe sets using GAPDH as the internal control. Aph1B protein content is measured by Western blot analysis of the soluble and membrane fractions with a polyclonal antibody (Santa Cruz; sc-49358).

Aβ40 and Aβ42 levels in hippocampus and cortex are measured in both the soluble and membrane fractions using sandwich ELISA with antibodies against human Aβ40 (2G3antibody) and human Aβ42 (21F12 antibody), both detected with biotin-3D6 antibody (Kanekivo et al., 2009, J. Biol. Chem. 284:33352-33359)

In addition, extracts from the various brain sections are also be probed for changes in activated Notch intracellular domain (NICD), the well documented released product of Notch cleavage by γ-secretase. Another known non-amyloidal substrate of γ-secretase is N-cadherin. Western blot analysis will be used to measure levels of NICD (Cell Signaling) and N-cadherin (Santa Cruz; sc-7939).

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

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uaugcucaau aggauua                                                 17


<210> SEQ ID NO 24
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 24

augcucaaua ggauuac                                                 17


<210> SEQ ID NO 25
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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ugcucaauag gauuacg                                                 17


<210> SEQ ID NO 26
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 26

gcucaauagg auuacgu                                                 17


<210> SEQ ID NO 27
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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cucaauagga uuacgua                                                   17


<210> SEQ ID NO 28
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 28

ucaauaggau uacguau                                                   17


<210> SEQ ID NO 29
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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augcucaaua ggauuacg                                                  18


<210> SEQ ID NO 30
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<212> TYPE: RNA
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gcuaugcuca auaggauu                                                  18


<210> SEQ ID NO 31
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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cuaugcucaa uaggauua                                                  18


<210> SEQ ID NO 32
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uaugcucaau aggauuac                                                  18


<210> SEQ ID NO 33
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 33

ugcucaauag gauuacgu                                                  18
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 34

gcucaauagg auuacgua                                                  18


<210> SEQ ID NO 35
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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cucaauagga uuacguau                                                  18


<210> SEQ ID NO 36
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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gcuaugcuca auaggauua                                                 19


<210> SEQ ID NO 37
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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cuaugcucaa uaggauuac                                                 19


<210> SEQ ID NO 38
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 38

uaugcucaau aggauuacg                                                 19


<210> SEQ ID NO 39
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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augcucaaua ggauuacgu                                                 19


<210> SEQ ID NO 40
<211> LENGTH: 19
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 40

ugcucaauag gauuacgua 19

<210> SEQ ID NO 41
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 41

gcucaauagg auuacguau 19

<210> SEQ ID NO 42
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

gcuaugcuca auaggauuac 20

<210> SEQ ID NO 43
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<212> TYPE: RNA
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<400> SEQUENCE: 43

cuaugcucaa uaggauuacg 20

<210> SEQ ID NO 44
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<212> TYPE: RNA
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uaugcucaau aggauuacgu 20

<210> SEQ ID NO 45
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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augcucaaua ggauuacgua 20

<210> SEQ ID NO 46
<211> LENGTH: 20
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

ugcucaauag gauuacguau 20

<210> SEQ ID NO 47
<211> LENGTH: 21
<212> TYPE: RNA

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 47

gcuaugcuca auaggauuac g                                              21


<210> SEQ ID NO 48
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 48

cuaugcucaa uaggauuacg u                                              21


<210> SEQ ID NO 49
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 49

uaugcucaau aggauuacgu a                                              21


<210> SEQ ID NO 50
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

augcucaaua ggauuacgua u                                              21


<210> SEQ ID NO 51
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 51

gcuaugcuca auaggauuac gu                                             22


<210> SEQ ID NO 52
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52

cuaugcucaa uaggauuacg ua                                             22


<210> SEQ ID NO 53
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

uaugcucaau aggauuacgu au                                             22
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

gcuaugcuca auaggauuac gua                                          23


<210> SEQ ID NO 55
<211> LENGTH: 23
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

cuaugcucaa uaggauuacg uau                                          23


<210> SEQ ID NO 56
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

gcuaugcuca auaggauuac guau                                         24


<210> SEQ ID NO 57
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

uacaggcguu cuucacgugg gaaa                                         24


<210> SEQ ID NO 58
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 58

uuacaggcgu ucuucacgug ggaa                                         24


<210> SEQ ID NO 59
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59

uuuacaggcg uucuucacgu ggga                                         24


<210> SEQ ID NO 60
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 60

guuuacaggc guucuucacg uggg                                              24


<210> SEQ ID NO 61
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61

gguuuacagg cguucuucac gugg                                              24


<210> SEQ ID NO 62
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62

agguuuacag gcguucuuca cgug                                              24


<210> SEQ ID NO 63
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63

aagguuuaca ggcguucuuc acgu                                              24


<210> SEQ ID NO 64
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 64

caagguuuac aggcguucuu cacg                                              24


<210> SEQ ID NO 65
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

gcaagguuua caggcguucu ucac                                              24


<210> SEQ ID NO 66
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

ugcaagguuu acaggcguuc uuca                                              24


<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

cugcaagguu uacaggcguu cuuc                                              24


<210> SEQ ID NO 68
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 68

acugcaaggu uuacaggcgu ucuu                                              24


<210> SEQ ID NO 69
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 69

uacugcaagg uuuacaggcg uucu                                              24


<210> SEQ ID NO 70
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 70

auacugcaag guuuacaggc guuc                                              24


<210> SEQ ID NO 71
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 71

aauacugcaa gguuuacagg cguu                                              24


<210> SEQ ID NO 72
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 72

caauacugca agguuuacag gcgu                                              24


<210> SEQ ID NO 73
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 73

ucaauacugc aagguuuaca ggcg                                              24
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<210> SEQ ID NO 74
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 74

acaggcguuc uucacguggg aaa 23

<210> SEQ ID NO 75
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75

uacaggcguu cuucacgugg gaa 23

<210> SEQ ID NO 76
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76

uuacaggcgu ucuucacgug gga 23

<210> SEQ ID NO 77
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

uuuacaggcg uucuucacgu ggg 23

<210> SEQ ID NO 78
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 78

guuuacaggc guucuucacg ugg 23

<210> SEQ ID NO 79
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

gguuuacagg cguucuucac gug 23

<210> SEQ ID NO 80
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 80

agguuuacag gcguucuuca cgu                                               23


<210> SEQ ID NO 81
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 81

aagguuuaca ggcguucuuc acg                                               23


<210> SEQ ID NO 82
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

caagguuuac aggcguucuu cac                                               23


<210> SEQ ID NO 83
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 83

gcaagguuua caggcguucu uca                                               23


<210> SEQ ID NO 84
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 84

ugcaagguuu acaggcguuc uuc                                               23


<210> SEQ ID NO 85
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 85

cugcaagguu uacaggcguu cuu                                               23


<210> SEQ ID NO 86
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 86

acugcaaggu uuacaggcgu ucu                                               23


<210> SEQ ID NO 87
<211> LENGTH: 23
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 87

uacugcaagg uuuacaggcg uuc                                               23


<210> SEQ ID NO 88
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 88

auacugcaag guuuacaggc guu                                               23


<210> SEQ ID NO 89
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 89

aauacugcaa gguuuacagg cgu                                               23


<210> SEQ ID NO 90
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 90

caauacugca agguuuacag gcg                                               23


<210> SEQ ID NO 91
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 91

ucaauacugc aagguuuaca ggc                                               23


<210> SEQ ID NO 92
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 92

caggcguucu ucacguggga aa                                                22


<210> SEQ ID NO 93
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 93

acaggcguuc uucacguggg aa                                                22
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<210> SEQ ID NO 94
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94

uacaggcguu cuucacgugg ga                                              22


<210> SEQ ID NO 95
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95

uuacaggcgu ucuucacgug gg                                              22


<210> SEQ ID NO 96
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96

uuuacaggcg uucuucacgu gg                                              22


<210> SEQ ID NO 97
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 97

guuuacaggc guucuucacg ug                                              22


<210> SEQ ID NO 98
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 98

gguuuacagg cguucuucac gu                                              22


<210> SEQ ID NO 99
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 99

agguuuacag gcguucuuca cg                                              22


<210> SEQ ID NO 100
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 100

aagguuuaca ggcguucuuc ac                                              22


<210> SEQ ID NO 101
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

caagguuuac aggcguucuu ca                                              22


<210> SEQ ID NO 102
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 102

gcaagguuua caggcguucu uc                                              22


<210> SEQ ID NO 103
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 103

ugcaagguuu acaggcguuc uu                                              22


<210> SEQ ID NO 104
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104

cugcaagguu uacaggcguu cu                                              22


<210> SEQ ID NO 105
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 105

acugcaaggu uuacaggcgu uc                                              22


<210> SEQ ID NO 106
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 106

uacugcaagg uuuacaggcg uu                                              22


<210> SEQ ID NO 107
<211> LENGTH: 22
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 107

auacugcaag guuuacaggc gu                                              22


<210> SEQ ID NO 108
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 108

aauacugcaa gguuuacagg cg                                              22


<210> SEQ ID NO 109
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 109

caauacugca agguuuacag gc                                              22


<210> SEQ ID NO 110
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 110

ucaauacugc aagguuuaca gg                                              22


<210> SEQ ID NO 111
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 111

aggcguucuu cacgugggaa a                                               21


<210> SEQ ID NO 112
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 112

caggcguucu ucacguggga a                                               21


<210> SEQ ID NO 113
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

acaggcguuc uucacguggg a                                               21
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<210> SEQ ID NO 114
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

uacaggcguu cuucacgugg g                                               21


<210> SEQ ID NO 115
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

uuacaggcgu ucuucacgug g                                               21


<210> SEQ ID NO 116
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 116

uuuacaggcg uucuucacgu g                                               21


<210> SEQ ID NO 117
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 117

guuuacaggc guucuucacg u                                               21


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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 118

gguuuacagg cguucuucac g                                               21


<210> SEQ ID NO 119
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 119

agguuuacag gcguucuuca c                                               21


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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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aagguuuaca ggcguucuuc a                                                21


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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 121

caagguuuac aggcguucuu c                                                21


<210> SEQ ID NO 122
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 122

gcaagguuua caggcguucu u                                                21


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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 123

ugcaagguuu acaggcguuc u                                                21


<210> SEQ ID NO 124
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 124

cugcaagguu uacaggcguu c                                                21


<210> SEQ ID NO 125
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 125

acugcaaggu uuacaggcgu u                                                21


<210> SEQ ID NO 126
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 126

uacugcaagg uuuacaggcg u                                                21


<210> SEQ ID NO 127
<211> LENGTH: 21
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 127

auacugcaag guuuacaggc g 21

<210> SEQ ID NO 128
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

aauacugcaa gguuuacagg c 21

<210> SEQ ID NO 129
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129

caauacugca agguuuacag g 21

<210> SEQ ID NO 130
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

ucaauacugc aagguuuaca g 21

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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

ggcguucuuc acgugggaaa 20

<210> SEQ ID NO 132
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

aggcguucuu cacgugggaa 20

<210> SEQ ID NO 133
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<212> TYPE: RNA
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caggcguucu ucacguggga 20

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acaggcguuc uucacguggg                                              20


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uacaggcguu cuucacgugg                                              20


<210> SEQ ID NO 136
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 136

uuacaggcgu ucuucacgug                                              20


<210> SEQ ID NO 137
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 137

uuuacaggcg uucuucacgu                                              20


<210> SEQ ID NO 138
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 138

guuuacaggc guucuucacg                                              20


<210> SEQ ID NO 139
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 139

gguuuacagg cguucuucac                                              20


<210> SEQ ID NO 140
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 140

agguuuacag gcguucuuca 20

<210> SEQ ID NO 141
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

aagguuuaca ggcguucuuc 20

<210> SEQ ID NO 142
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

caagguuuac aggcguucuu 20

<210> SEQ ID NO 143
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 143

gcaagguuua caggcguucu 20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 144

ugcaagguuu acaggcguuc 20

<210> SEQ ID NO 145
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 145

cugcaagguu uacaggcguu 20

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 146

acugcaaggu uuacaggcgu 20

<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 147

uacugcaagg uuuacaggcg                                                  20


<210> SEQ ID NO 148
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 148

auacugcaag guuuacaggc                                                  20


<210> SEQ ID NO 149
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 149

aauacugcaa gguuuacagg                                                  20


<210> SEQ ID NO 150
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 150

gcguucuuca cgugggaaa                                                   19


<210> SEQ ID NO 151
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<212> TYPE: RNA
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<400> SEQUENCE: 151

ggcguucuuc acgugggaa                                                   19


<210> SEQ ID NO 152
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 152

aggcguucuu cacguggga                                                   19


<210> SEQ ID NO 153
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

caggcguucu ucacguggg                                                   19
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

acaggcguuc uucacgugg                                                  19


<210> SEQ ID NO 155
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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uacaggcguu cuucacgug                                                  19


<210> SEQ ID NO 156
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 156

uuacaggcgu ucuucacgu                                                  19


<210> SEQ ID NO 157
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 157

uuuacaggcg uucuucacg                                                  19


<210> SEQ ID NO 158
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 158

guuuacaggc guucuucac                                                  19


<210> SEQ ID NO 159
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 159

gguuuacagg cguucuuca                                                  19


<210> SEQ ID NO 160
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic
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agguuuacag gcguucuuc                                                    19


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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 161

aagguuuaca ggcguucuu                                                    19


<210> SEQ ID NO 162
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 162

caagguuuac aggcguucu                                                    19


<210> SEQ ID NO 163
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 163

gcaagguuua caggcguuc                                                    19


<210> SEQ ID NO 164
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<212> TYPE: RNA
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<400> SEQUENCE: 164

ugcaagguuu acaggcguu                                                    19


<210> SEQ ID NO 165
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

cugcaagguu uacaggcgu                                                    19


<210> SEQ ID NO 166
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

acugcaaggu uuacaggcg                                                    19


<210> SEQ ID NO 167
<211> LENGTH: 19
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167

uacugcaagg uuuacaggc                                                    19


<210> SEQ ID NO 168
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

auacugcaag guuuacagg                                                    19


<210> SEQ ID NO 169
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169

cguucuucac gugggaaa                                                     18


<210> SEQ ID NO 170
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 170

gcguucuuca cgugggaa                                                     18


<210> SEQ ID NO 171
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 171

ggcguucuuc acguggga                                                     18


<210> SEQ ID NO 172
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 172

aggcguucuu cacguggg                                                     18


<210> SEQ ID NO 173
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 173

caggcguucu ucacgugg                                                     18
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 174

acaggcguuc uucacgug                                                  18


<210> SEQ ID NO 175
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 175

uacaggcguu cuucacgu                                                  18


<210> SEQ ID NO 176
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 176

uuacaggcgu ucuucacg                                                  18


<210> SEQ ID NO 177
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 177

uuuacaggcg uucuucac                                                  18


<210> SEQ ID NO 178
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 178

guuuacaggc guucuuca                                                  18


<210> SEQ ID NO 179
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 179

gguuuacagg cguucuuc                                                  18


<210> SEQ ID NO 180
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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agguuuacag gcguucuu                                                     18


<210> SEQ ID NO 181
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 181

aagguuuaca ggcguucu                                                     18


<210> SEQ ID NO 182
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 182

caagguuuac aggcguuc                                                     18


<210> SEQ ID NO 183
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 183

gcaagguuua caggcguu                                                     18


<210> SEQ ID NO 184
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 184

ugcaagguuu acaggcgu                                                     18


<210> SEQ ID NO 185
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 185

cugcaagguu uacaggcg                                                     18


<210> SEQ ID NO 186
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 186

acugcaaggu uuacaggc                                                     18


<210> SEQ ID NO 187
<211> LENGTH: 18
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 187

uacugcaagg uuuacagg                                              18


<210> SEQ ID NO 188
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 188

cuagguuuac gggaccucuu caac                                       24


<210> SEQ ID NO 189
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

gcuagguuua cgggaccucu ucaa                                       24


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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

cgcuagguuu acgggaccuc uuca                                       24


<210> SEQ ID NO 191
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 191

ccgcuagguu uacgggaccu cuuc                                       24


<210> SEQ ID NO 192
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<212> TYPE: RNA
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<400> SEQUENCE: 192

accgcuaggu uuacgggacc ucuu                                       24


<210> SEQ ID NO 193
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 193

aaccgcuagg uuuacgggac cucu                                       24
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<210> SEQ ID NO 194
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 194

aaaccgcuag guuuacggga ccuc 24

<210> SEQ ID NO 195
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 195

aaaaccgcua gguuuacggg accu 24

<210> SEQ ID NO 196
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 196

uagguuuacg ggaccucuuc aac 23

<210> SEQ ID NO 197
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197

cuagguuuac gggaccucuu caa 23

<210> SEQ ID NO 198
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 198

gcuagguuua cgggaccucu uca 23

<210> SEQ ID NO 199
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 199

cgcuagguuu acgggaccuc uuc 23

<210> SEQ ID NO 200
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 200

ccgcuagguu uacgggaccu cuu                                               23


<210> SEQ ID NO 201
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

accgcuaggu uuacgggacc ucu                                               23


<210> SEQ ID NO 202
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 202

aaccgcuagg uuuacgggac cuc                                               23


<210> SEQ ID NO 203
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 203

aaaccgcuag guuuacggga ccu                                               23


<210> SEQ ID NO 204
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 204

aaaaccgcua gguuuacggg acc                                               23


<210> SEQ ID NO 205
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 205

agguuuacgg gaccucuuca ac                                                22


<210> SEQ ID NO 206
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 206

uagguuuacg ggaccucuuc aa                                                22


<210> SEQ ID NO 207
<211> LENGTH: 22
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 207

cuagguuuac gggaccucuu ca                                              22


<210> SEQ ID NO 208
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<212> TYPE: RNA
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<400> SEQUENCE: 208

gcuagguuua cgggaccucu uc                                              22


<210> SEQ ID NO 209
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 209

cgcuagguuu acgggaccuc uu                                              22


<210> SEQ ID NO 210
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<212> TYPE: RNA
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ccgcuagguu uacgggaccu cu                                              22


<210> SEQ ID NO 211
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<212> TYPE: RNA
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accgcuaggu uuacgggacc uc                                              22


<210> SEQ ID NO 212
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<212> TYPE: RNA
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gguuuacggg accucuucaa c 21

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cuagguuuac gggaccucuu c 21

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gcuagguuua cgggaccucu u 21

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aaccgcuagg uuuacgggac c                                              21


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cgcuagguuu acgggaccuc 20

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guuuacggga ccucuucaa 19

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gguuuacggg accucuuca                                                19


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agguuuacgg gaccucuuc                                                19


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uagguuuacg ggaccucuu                                                19


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cuagguuuac gggaccucu                                                19


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gcuagguuua cgggaccuc                                                19


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cgcuagguuu acgggaccu                                                19


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uuuacgggac cucuucaa                                                     18


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guuuacggga ccucuuca                                                     18


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uagguuuacg ggaccucu                                                     18


<210> SEQ ID NO 247
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cuagguuuac gggaccuc 18

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gcuagguuua cgggaccu 18

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cgcuagguuu acgggacc 18

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uuacuuccgg aguccuugcu ucca 24

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cuuacuuccg gaguccuugc uucc 24

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ccuuacuucc ggaguccuug cuuc 24

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accuuacuuc cggaguccuu gcuu 24

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ugaccuuacu uccggagucc uugc                                            24


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cugaccuuac uuccggaguc cuug                                            24


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cuuacuuccg gaguccuugc uuc                                             23


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ccuuacuucc ggaguccuug cuu                                              23


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gaccuuacuu ccggaguccu ugc                                              23


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ugaccuuacu uccggagucc uug                                              23


<210> SEQ ID NO 264
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<212> TYPE: RNA
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cuuacuuccg gaguccuugc uu                                              22


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acugaccuua cuuccggagu cc                                              22
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uuacuuccgg aguccuugcu u                                              21


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cuuacuuccg gaguccuugc u                                              21


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ccuuacuucc ggaguccuug c                                              21


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accuuacuuc cggaguccuu g                                              21


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gaccuuacuu ccggaguccu u                                              21


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ugaccuuacu uccggagucc u                                              21


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accuuacuuc cggaguccuu                                                20


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gaccuuacuu ccggaguccu                                                20


<210> SEQ ID NO 287
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<212> TYPE: RNA
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ugaccuuacu uccggagucc                                                    20


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cuuacuuccg gaguccuug                                                     19


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ccuuacuucc ggaguccuu                                                     19


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accuuacuuc cggaguccu                                                     19
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gaccuuacuu ccggagucc                                                  19


<210> SEQ ID NO 295
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ugaccuuacu uccggaguc                                                  19


<210> SEQ ID NO 296
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cugaccuuac uuccggagu                                                  19


<210> SEQ ID NO 297
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cuuacuuccg gaguccuu                                                   18


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ccuuacuucc ggaguccu                                                    18


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accuuacuuc cggagucc                                                    18


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gaccuuacuu ccggaguc                                                    18


<210> SEQ ID NO 303
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ugaccuuacu uccggagu                                                    18


<210> SEQ ID NO 304
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cugaccuuac uuccggag                                                    18


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<400> SEQUENCE: 306

uuuucagcuu gucuuagacg ccuu                                             24


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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 307

uuucagcuug ucuuagacgc cuu 23

<210> SEQ ID NO 308
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uuuucagcuu gucuuagacg ccu 23

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uucagcuugu cuuagacgcc uu 22

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uuuucagcuu gucuuagacg cc 22

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ucagcuuguc uuagacgccu u 21

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uucagcuugu cuuagacgcc u 21

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uuuucagcuu gucuuagacg c                                                 21


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ucagcuuguc uuagacgcc 19

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uuucagcuug ucuuagacg 19

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uucagcuugu cuuagacg                                                 18


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uuucagcuug ucuuagac                                                 18


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ucagcuuguc uaagaugccu uguu                                           24


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uucagcuugu cuaagaugcc uugu                                           24


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uuucagcuug ucuaagaugc cuug                                           24


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uuuucagcuu gucuaagaug ccuu                                           24


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cagcuugucu aagaugccuu guu                                            23


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ucagcuuguc uaagaugccu ugu                                            23


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uucagcuugu cuaagaugcc uug 23

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uuucagcuug ucuaagaugc cuu 23

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uuuucagcuu gucuaagaug ccu 23

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agcuugucua agaugccuug uu 22

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cagcuugucu aagaugccuu gu 22

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ucagcuuguc uaagaugccu ug 22

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uucagcuugu cuaagaugcc uu 22

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uuucagcuug ucuaagaugc cu 22

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uuuucagcuu gucuaagaug cc 22

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gcuugucuaa gaugccuugu u 21

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agcuugucua agaugccuug u 21

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cagcuugucu aagaugccuu g 21

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ucagcuuguc uaagaugccu u 21

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uucagcuugu cuaagaugcc u 21

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uuuucagcuu gucuaagaug c                                                21


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cuugucuaag augccuuguu                                                  20


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<210> SEQ ID NO 366
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gcuugucuaa gaugccuu                                                     18


<210> SEQ ID NO 367
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<212> TYPE: RNA
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<220> FEATURE:
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ucguaccacc auuugcuuuu ca                                               22


<210> SEQ ID NO 371
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ucguaccacc auuugcuuuu c                                                21


<210> SEQ ID NO 373
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cguaccacca uuugcuuuuc                                                  20


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<212> TYPE: RNA
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<400> SEQUENCE: 376

uaagaugccu uguucacuga guuu                                             24


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aagaugccuu guucacugag uuu                                              23


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uaagaugccu uguucacuga guu                                              23


<210> SEQ ID NO 379
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agaugccuug uucacugagu uu                                               22


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aagaugccuu guucacugag uu 22

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uaagaugccu uguucacuga gu 22

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gaugccuugu ucacugaguu u 21

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agaugccuug uucacugagu u 21

<210> SEQ ID NO 384
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aagaugccuu guucacugag u 21

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uaagaugccu uguucacuga g 21

<210> SEQ ID NO 386
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augccuuguu cacugaguuu 20

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<212> TYPE: RNA

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gaugccuugu ucacugaguu                                                   20


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<400> SEQUENCE: 388

agaugccuug uucacugagu                                                   20


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aagaugccuu guucacugag                                                   20


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uaagaugccu uguucacuga                                                   20


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ugccuuguuc acugaguuu                                                    19


<210> SEQ ID NO 392
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<223> OTHER INFORMATION: Synthetic

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augccuuguu cacugaguu                                                    19


<210> SEQ ID NO 393
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gaugccuugu ucacugagu                                                    19
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<400> SEQUENCE: 394

agaugccuug uucacugag                                                   19


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<400> SEQUENCE: 395

aagaugccuu guucacuga                                                   19


<210> SEQ ID NO 396
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uaagaugccu uguucacug                                                   19


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<212> TYPE: RNA
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ugccuuguuc acugaguu                                                    18


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augccuuguu cacugagu                                                    18


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gaugccuugu ucacugag                                                    18


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<220> FEATURE:
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<400> SEQUENCE: 401

caagauuuac uggguucuu cacg 24

<210> SEQ ID NO 402
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 402

gcaagauuua cuggguucu ucac 24

<210> SEQ ID NO 403
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<212> TYPE: RNA
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<400> SEQUENCE: 403

ugcaagauuu acuggguuc uuca 24

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cugcaagauu uacugggguu cuu 23

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acugcaagau uuacuggggu ucu 23

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uacugcaaga uuuacugggg uuc 23

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auacugcaag auuuacuggg guu 23

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cugcaagauu uacugggguu cu                                            22


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acugcaagau uuacuggggu uc                                            22


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uacugcaaga uuuacugggg uu                                            22


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gauuuacugg gguucuucac g                                               21


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gcaagauuua cugggguucu u                                               21


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cugcaagauu uacugggguu c 21

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acugcaagau uuacuggggu u 21

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uacugcaaga uuuacugggg u 21

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auuuacuggg guucuucacg 20

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gauuuacugg gguucuucac 20

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caagauuuac ugggguucuu 20

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gcaagauuua cugggguucu 20

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ugcaagauuu acugggguuc 20

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cugcaagauu uacugggguu 20

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acugcaagau uuacuggggu 20

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uuuacugggg uucuucacg 19

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<212> TYPE: RNA

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<400> SEQUENCE: 447

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gauuuacugg gguucuuca                                                19


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caagauuuac ugggguucu                                                19


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ugcaagauuu acugggguu                                                19
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<212> TYPE: RNA
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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gauuuacugg gguucuuc                                                   18


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gcaagauuua cuggggguu                                                   18


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ugcaagauuu acuggggu                                                    18


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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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caagguuuac aggaguucuu cacg                                             24


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gcaagguuua cuggaguucu ucac                                             24


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<400> SEQUENCE: 466

ggcaagguuu acuggaguuc uuca                                             24


<210> SEQ ID NO 467
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 467

cggcaagguu uacuggaguu cuuc                                              24


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acggcaaggu uuacuggagu ucuu                                              24


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aacggcaagg uuuacuggag uucu                                              24


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aaacggcaag guuuacugga guuc                                              24


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aaaacggcaa gguuuacugg aguu                                              24


<210> SEQ ID NO 472
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<400> SEQUENCE: 472

caaaacggca agguuuacug gagu                                              24


<210> SEQ ID NO 473
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<212> TYPE: RNA
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<400> SEQUENCE: 473

aagguuuaca ggaguucuuc acg                                               23
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<400> SEQUENCE: 474

caagguuuac uggaguucuu cac 23

<210> SEQ ID NO 475
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<212> TYPE: RNA
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gcaagguuua cuggaguucu uca 23

<210> SEQ ID NO 476
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<212> TYPE: RNA
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<400> SEQUENCE: 476

ggcaagguuu acuggaguuc uuc 23

<210> SEQ ID NO 477
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<212> TYPE: RNA
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<400> SEQUENCE: 477

cggcaagguu uacuggaguu cuu 23

<210> SEQ ID NO 478
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<400> SEQUENCE: 478

acggcaaggu uuacuggagu ucu 23

<210> SEQ ID NO 479
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<212> TYPE: RNA
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aacggcaagg uuuacuggag uuc 23

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aaacggcaag guuuacugga guu                                              23


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<400> SEQUENCE: 481

aaaacggcaa gguuuacugg agu                                              23


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<220> FEATURE:
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agguuuacag gaguucuuca cg                                               22


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<400> SEQUENCE: 483

aagguuuacu ggaguucuuc ac                                               22


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<400> SEQUENCE: 484

caagguuuac uggaguucuu ca                                               22


<210> SEQ ID NO 485
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gcaagguuua cuggaguucu uc                                               22


<210> SEQ ID NO 486
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<400> SEQUENCE: 486

ggcaagguuu acuggaguuc uu                                               22


<210> SEQ ID NO 487
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 487

cggcaagguu uacuggaguu cu                                              22


<210> SEQ ID NO 488
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acggcaaggu uuacuggagu uc                                              22


<210> SEQ ID NO 489
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aacggcaagg uuuacuggag uu                                              22


<210> SEQ ID NO 490
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<400> SEQUENCE: 490

aaacggcaag guuuacugga gu                                              22


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<400> SEQUENCE: 491

gguuuacagg aguucuucac g                                               21


<210> SEQ ID NO 492
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<212> TYPE: RNA
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<400> SEQUENCE: 492

agguuuacug gaguucuuca c                                               21


<210> SEQ ID NO 493
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<223> OTHER INFORMATION: Synthetic

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aagguuuacu ggaguucuuc a                                               21
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caagguuuac uggaguucuu c                                              21


<210> SEQ ID NO 495
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gcaagguuua cuggaguucu u                                              21


<210> SEQ ID NO 496
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ggcaagguuu acuggaguuc u                                              21


<210> SEQ ID NO 497
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cggcaagguu uacuggaguu c                                              21


<210> SEQ ID NO 498
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acggcaaggu uuacuggagu u                                              21


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<210> SEQ ID NO 507
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<212> TYPE: RNA
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uuacaggagu ucuucacg 18

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uuuacuggag uucuucac 18

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gcaagguuua cuggaguu                                                18


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<212> TYPE: RNA
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<212> TYPE: RNA
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acaguacugu cuucacuguc agcu                                            24


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uacaguacug ucuucacugu cagc                                            24


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ucuucgucac ugccuucauu uucu                                            24


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acaucaguuu caaugucuuc guca                                            24


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caguacuguc uucacuguca gcu                                             23


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cuucgucacu gccuucauuu ucu                                             23


<210> SEQ ID NO 537
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<400> SEQUENCE: 537

ucuucgucac ugccuucauu uuc                                             23


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acaucaguuu caaugucuuc guc                                               23


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<400> SEQUENCE: 541

aacucacugc uguauugaug agg                                               23


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<400> SEQUENCE: 542

guacugucuu cacugucagc ug                                                22


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<212> TYPE: RNA
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<212> TYPE: RNA
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<400> SEQUENCE: 544

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uucgucacug ccuucauuuu cu                                                22


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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 546

cuucgucacu gccuucauuu uc                                                22


<210> SEQ ID NO 547
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<212> TYPE: RNA
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<400> SEQUENCE: 547

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<220> FEATURE:
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aucaguuuca augucuucgu ca                                              22


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caucaguuuc aaugucuucg uc                                              22


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<220> FEATURE:
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acaucaguuu caaugucuuc gu                                              22


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<212> TYPE: RNA
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<400> SEQUENCE: 552

acucacugcu guauugauga gg                                              22


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<212> TYPE: RNA
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<400> SEQUENCE: 553

aacucacugc uguauugaug ag                                              22
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guacugucuu cacugucagc u                                               21


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ucgucacugc cuucauuuuc u                                               21


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cuucgucacu gccuucauuu u                                               21


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<210> SEQ ID NO 562
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<223> OTHER INFORMATION: Synthetic

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<212> TYPE: RNA
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<220> FEATURE:
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<210> SEQ ID NO 564
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 564

caucaguuuc aaugucuucg u                                              21


<210> SEQ ID NO 565
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 565

acaucaguuu caaugucuuc g                                              21


<210> SEQ ID NO 566
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 566

cucacugcug uauugaugag g                                              21


<210> SEQ ID NO 567
<211> LENGTH: 21
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 567

acucacugcu guauugauga g                                              21


<210> SEQ ID NO 568
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 568

aacucacugc uguauugaug a                                              21


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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 569

acugucuuca cugucagcug                                                20


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<400> SEQUENCE: 570

uacugucuuc acugucagcu                                                20


<210> SEQ ID NO 571
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<212> TYPE: RNA
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<400> SEQUENCE: 571

guacugucuu cacugucagc                                                20


<210> SEQ ID NO 572
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 572

cgucacugcc uucauuuucu                                                20


<210> SEQ ID NO 573
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 573

ucgucacugc cuucauuuuc                                                20
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<400> SEQUENCE: 574

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cuucgucacu gccuucauuu                                                  20


<210> SEQ ID NO 576
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<212> TYPE: RNA
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<400> SEQUENCE: 576

ucuucgucac ugccuucauu                                                  20


<210> SEQ ID NO 577
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<220> FEATURE:
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<400> SEQUENCE: 577

aguuucaaug ucuucgucac                                                  20


<210> SEQ ID NO 578
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 578

caguuucaau gucuucguca                                                  20


<210> SEQ ID NO 579
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<212> TYPE: RNA
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ucaguuucaa ugucuucguc                                                  20


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<212> TYPE: RNA
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aucaguuuca augucuucg                                                    19


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<220> FEATURE:
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<400> SEQUENCE: 582

acaucaguuu caaugucuuc                                                   20


<210> SEQ ID NO 583
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 583

ucacugcugu auugaugagg                                                   20


<210> SEQ ID NO 584
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<212> TYPE: RNA
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<400> SEQUENCE: 584

cucacugcug uauugaugag                                                   20


<210> SEQ ID NO 585
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<212> TYPE: RNA
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<400> SEQUENCE: 585

acucacugcu guauugauga                                                   20


<210> SEQ ID NO 586
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aacucacugc uguauugaug                                                   20


<210> SEQ ID NO 587
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

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acugucuuca cugucagcu 19

<210> SEQ ID NO 589
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 589

uacugucuuc acugucagc 19

<210> SEQ ID NO 590
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 590

gucacugccu ucauuuucu 19

<210> SEQ ID NO 591
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 591

cgucacugcc uucauuuuc 19

<210> SEQ ID NO 592
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 592

ucgucacugc cuucauuuu 19

<210> SEQ ID NO 593
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 593

uucgucacug ccuucauuu 19

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cuucgucacu gccuucauu                                               19


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ucuucgucac ugccuucau                                               19


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acucacugcu guauugaug                                               19


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aacucacugc uguauugau 19

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cuucacuguc agcuguga 18

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ugucuucacu gucagcug 18

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<212> TYPE: RNA
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cugucuucac ugucagcu 18

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<212> TYPE: RNA
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acugucuuca cugucagc 18

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ucuucgucac ugccuuca 18

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<400> SEQUENCE: 606

acugcuguau ugaugagg 18

<210> SEQ ID NO 607
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<400> SEQUENCE: 607

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cucacugcug uauugaug                                                    18


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acucacugcu guauugau                                                    18


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aacucacugc uguauuga                                                    18


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accuaaccac uguacaaaag auuu                                             24


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uaccuaacca cuguacaaaa gauu                                             24
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cuaccuaacc acuguacaaa agau                                            24


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ccuaccuaac cacuguacaa aaga                                            24


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accuaccuaa ccacuguaca aaag                                            24


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accuaaccac uguacaaaag auu                                             23


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uaccuaacca cuguacaaaa gau                                             23


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cuaccuaacc acuguacaaa aga                                             23


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<212> TYPE: RNA
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ccuaccuaac cacuguacaa aag                                               23


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accuaccuaa ccacuguaca aaa                                               23


<210> SEQ ID NO 622
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accuaaccac uguacaaaag au                                                22


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uaccuaacca cuguacaaaa ga                                                22


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<212> TYPE: RNA
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cuaccuaacc acuguacaaa ag                                                22


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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 625

ccuaccuaac cacuguacaa aa                                                22


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<212> TYPE: RNA
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<400> SEQUENCE: 626

accuaccuaa ccacuguaca aa                                                22


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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 627

uguacaaaag auuucaccau ag 22

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<400> SEQUENCE: 628

accuaaccac uguacaaaag a 21

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uaccuaacca cuguacaaaa g 21

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cuaccuaacc acuguacaaa a 21

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<400> SEQUENCE: 631

ccuaccuaac cacuguacaa a 21

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<400> SEQUENCE: 632

accuaccuaa ccacuguaca a 21

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 633

guacaaaaga uuucaccaua g 21

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uguacaaaag auuucaccau a                                              21


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accuaaccac uguacaaaag                                                20


<210> SEQ ID NO 636
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cuaccuaacc acuguacaaa                                                20


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<212> TYPE: RNA
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<400> SEQUENCE: 638

ccuaccuaac cacuguacaa                                                20


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accuaccuaa ccacuguaca                                                20


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<212> TYPE: RNA
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uacaaaagau uucaccauag                                                20


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guacaaaaga uuucaccaua                                                20


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uguacaaaag auuucaccau                                                20


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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 643

accuaaccac uguacaaaa                                                 19


<210> SEQ ID NO 644
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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uaccuaacca cuguacaaa                                                 19


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<212> TYPE: RNA
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<400> SEQUENCE: 645

cuaccuaacc acuguacaa                                                 19


<210> SEQ ID NO 646
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 646

ccuaccuaac cacuguaca                                                 19


<210> SEQ ID NO 647
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 647

accuaccuaa ccacuguac 19

<210> SEQ ID NO 648
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 648

acaaaagauu ucaccauag 19

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 649

uacaaaagau uucaccaua 19

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<212> TYPE: RNA
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<400> SEQUENCE: 650

guacaaaaga uuucaccau 19

<210> SEQ ID NO 651
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 651

uguacaaaag auuucacca 19

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<212> TYPE: RNA
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<400> SEQUENCE: 652

accuaaccac uguacaaa 18

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<220> FEATURE:
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uaccuaacca cuguacaa 18

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cuaccuaacc acuguaca                                                    18


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ccuaccuaac cacuguac                                                    18


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accuaccuaa ccacugua                                                    18


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caaaagauuu caccauag                                                    18


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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 658

acaaaagauu ucaccaua                                                    18


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uacaaaagau uucaccau                                                    18


<210> SEQ ID NO 660
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<223> OTHER INFORMATION: Synthetic
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guacaaaaga uuucacca                                                   18


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<220> FEATURE:
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<400> SEQUENCE: 661

uguacaaaag auuucacc                                                   18


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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 662

cagaaacuaa acaggaagaa aa                                              22


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ccagaaacua aacaggaaga aa                                              22


<210> SEQ ID NO 664
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<212> TYPE: RNA
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<220> FEATURE:
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ccagaaacua aacaggaaga a                                               21


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<212> TYPE: RNA
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<220> FEATURE:
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cagaaacuaa acaggaagaa                                                 20


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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 666

ccagaaacua aacaggaaga                                                 20


<210> SEQ ID NO 667
<211> LENGTH: 19
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 667

cagaaacuaa acaggaaga                                                19


<210> SEQ ID NO 668
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ccagaaacua aacaggaag                                                19


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<212> TYPE: RNA
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<220> FEATURE:
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ccagaaacua aacaggaa                                                 18


<210> SEQ ID NO 670
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<220> FEATURE:
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<400> SEQUENCE: 670

acuccacuca ugauuccaaa g                                             21


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<223> OTHER INFORMATION: Synthetic

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acuccacuca ugauuccaaa                                               20


<210> SEQ ID NO 672
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acuccacuca ugauuccaa                                                19


<210> SEQ ID NO 673
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 673

cuccacucau gauuccaa                                                 18
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cuccacucau gauuccaaag                                                  20


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<220> FEATURE:
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<400> SEQUENCE: 675

uacuccacuc augauuccaa                                                  20


<210> SEQ ID NO 676
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 676

auacuccacu caugauucca                                                  20


<210> SEQ ID NO 677
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 677

aauacuccac ucaugauucc                                                  20


<210> SEQ ID NO 678
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<400> SEQUENCE: 678

uccacucaug auuccaaag                                                   19


<210> SEQ ID NO 679
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 679

cuccacucau gauuccaaa                                                   19


<210> SEQ ID NO 680
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic
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uacuccacuc augauucca                                                19


<210> SEQ ID NO 681
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<212> TYPE: RNA
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auacuccacu caugauucc                                                19


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<400> SEQUENCE: 682

acuccacuca ugauucca                                                 18


<210> SEQ ID NO 683
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 683

uacuccacuc augauucc                                                 18


<210> SEQ ID NO 684
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 684

ugaaugccca cugugccugg                                               20


<210> SEQ ID NO 685
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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augaaugccc acugugccug                                               20


<210> SEQ ID NO 686
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<212> TYPE: RNA
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<400> SEQUENCE: 686

caugaaugcc cacugugccu                                               20


<210> SEQ ID NO 687
<211> LENGTH: 20
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 687

ccaugaaugc ccacugugcc                                                  20


<210> SEQ ID NO 688
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<212> TYPE: RNA
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<400> SEQUENCE: 688

gaaugcccac ugugccugg                                                   19


<210> SEQ ID NO 689
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<212> TYPE: RNA
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ugaaugccca cugugccug                                                   19


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augaaugccc acugugccu                                                   19


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caugaaugcc cacugugcc                                                   19


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ccaugaaugc ccacugugc                                                   19


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aaugcccacu gugccugg                                                    18
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gaaugcccac ugugccug                                                    18


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ugaaugccca cugugccu                                                    18


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<212> TYPE: RNA
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augaaugccc acugugcc                                                    18


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caugaaugcc cacugugc                                                    18


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<220> FEATURE:
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ccaugaaugc ccacugug                                                    18


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<212> TYPE: RNA
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cuaugagaca cauaccugaa ua                                               22


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<212> TYPE: RNA
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gcuaugagac acauaccuga au                                              22


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<212> TYPE: RNA
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agcuaugaga cacauaccug aa                                              22


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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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cagcuaugag acacauaccu ga                                              22


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<212> TYPE: RNA
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acagcuauga gacacauacc ug                                              22


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<212> TYPE: RNA
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gacagcuaug agacacauac cu                                              22


<210> SEQ ID NO 705
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<212> TYPE: RNA
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ugacagcuau gagacacaua cc                                              22


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uaugagacac auaccugaau a                                               21


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<220> FEATURE:
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cuaugagaca cauaccugaa u                                              21


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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 708

gcuaugagac acauaccuga a                                              21


<210> SEQ ID NO 709
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<223> OTHER INFORMATION: Synthetic

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agcuaugaga cacauaccug a                                              21


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<400> SEQUENCE: 710

cagcuaugag acacauaccu g                                              21


<210> SEQ ID NO 711
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<212> TYPE: RNA
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<400> SEQUENCE: 711

acagcuauga gacacauacc u                                              21


<210> SEQ ID NO 712
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<212> TYPE: RNA
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augagacaca uaccugaaua                                                20


<210> SEQ ID NO 713
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uaugagacac auaccugaau                                                20
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<210> SEQ ID NO 714
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cuaugagaca cauaccugaa 20

<210> SEQ ID NO 715
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gcuaugagac acauaccuga 20

<210> SEQ ID NO 716
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<212> TYPE: RNA
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<400> SEQUENCE: 716

agcuaugaga cacauaccug 20

<210> SEQ ID NO 717
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<212> TYPE: RNA
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<400> SEQUENCE: 717

cagcuaugag acacauaccu 20

<210> SEQ ID NO 718
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<212> TYPE: RNA
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<400> SEQUENCE: 718

acagcuauga gacacauacc 20

<210> SEQ ID NO 719
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<212> TYPE: RNA
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ugagacacau accugaaua 19

<210> SEQ ID NO 720
<211> LENGTH: 19
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 720

uaugagacac auaccugaa                                                    19


<210> SEQ ID NO 721
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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cuaugagaca cauaccuga                                                    19


<210> SEQ ID NO 722
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<212> TYPE: RNA
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gcuaugagac acauaccug                                                    19


<210> SEQ ID NO 723
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agcuaugaga cacauaccu                                                    19


<210> SEQ ID NO 724
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<212> TYPE: RNA
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cagcuaugag acacauacc                                                    19


<210> SEQ ID NO 725
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 725

cuaugagaca cauaccug                                                     18


<210> SEQ ID NO 726
<211> LENGTH: 18
<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

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gcuaugagac acauaccu                                                     18


<210> SEQ ID NO 727
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 727

agcuaugaga cacauacc                                                18


<210> SEQ ID NO 728
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 728

cacauaccug aau                                                     13


<210> SEQ ID NO 729
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 729

ugagcugagu caagcggagc uggc                                         24


<210> SEQ ID NO 730
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 730

gggaacugac cggugagcug agu                                          23


<210> SEQ ID NO 731
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 731

accggugagc ugagucaagc gg                                           22


<210> SEQ ID NO 732
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<212> TYPE: RNA
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<400> SEQUENCE: 732

gaccggugag cugagucaag cg                                           22


<210> SEQ ID NO 733
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 733

ugaccgguga gcugagucaa gc                                           22
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cugaccggug agcugaguca ag                                              22


<210> SEQ ID NO 735
<211> LENGTH: 22
<212> TYPE: RNA
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acugaccggu gagcugaguc aa                                              22


<210> SEQ ID NO 736
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<212> TYPE: RNA
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<400> SEQUENCE: 736

aacugaccgg ugagcugagu ca                                              22


<210> SEQ ID NO 737
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<212> TYPE: RNA
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gaacugaccg gugagcugag uc                                              22


<210> SEQ ID NO 738
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 738

ggaacugacc ggugagcuga gu                                              22


<210> SEQ ID NO 739
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<212> TYPE: RNA
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gggaacugac cggugagcug ag                                              22


<210> SEQ ID NO 740
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 740

accggugagc ugagucaagc g 21

<210> SEQ ID NO 741
<211> LENGTH: 21
<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 741

gaccggugag cugagucaag c 21

<210> SEQ ID NO 742
<211> LENGTH: 21
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 742

ugaccgguga gcugagucaa g 21

<210> SEQ ID NO 743
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 743

cugaccggug agcugaguca a 21

<210> SEQ ID NO 744
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 744

acugaccggu gagcugaguc a 21

<210> SEQ ID NO 745
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 745

aacugaccgg ugagcugagu c 21

<210> SEQ ID NO 746
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 746

gaacugaccg gugagcugag u 21

<210> SEQ ID NO 747
<211> LENGTH: 21
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 747

ggaacugacc ggugagcuga g                                              21


<210> SEQ ID NO 748
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 748

gggaacugac cggugagcug a                                              21


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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<210> SEQ ID NO 750
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 750

gaccggugag cugagucaag                                                20


<210> SEQ ID NO 751
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ugaccgguga gcugagucaa                                                20


<210> SEQ ID NO 752
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<400> SEQUENCE: 752

cugaccggug agcugaguca                                                20


<210> SEQ ID NO 753
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<212> TYPE: RNA
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acugaccggu gagcugaguc                                                20
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aacugaccgg ugagcugagu                                                  20


<210> SEQ ID NO 755
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gaacugaccg gugagcugag                                                  20


<210> SEQ ID NO 756
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<400> SEQUENCE: 756

ggaacugacc ggugagcuga                                                  20


<210> SEQ ID NO 757
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 757

gggaacugac cggugagcug                                                  20


<210> SEQ ID NO 758
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 758

accggugagc ugagucaag                                                   19


<210> SEQ ID NO 759
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<212> TYPE: RNA
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<400> SEQUENCE: 759

gaccggugag cugagucaa                                                   19


<210> SEQ ID NO 760
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<212> TYPE: RNA
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ugaccgguga gcugaguca                                                   19


<210> SEQ ID NO 761
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<212> TYPE: RNA
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cugaccggug agcugaguc                                                   19


<210> SEQ ID NO 762
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<212> TYPE: RNA
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acugaccggu gagcugagu                                                   19


<210> SEQ ID NO 763
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<400> SEQUENCE: 763

aacugaccgg ugagcugag                                                   19


<210> SEQ ID NO 764
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<400> SEQUENCE: 764

gaacugaccg gugagcuga                                                   19


<210> SEQ ID NO 765
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 765

ggaacugacc ggugagcug                                                   19


<210> SEQ ID NO 766
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 766

gggaacugac cggugagcu                                                   19


<210> SEQ ID NO 767
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 767

accggugagc ugagucaa                                                   18


<210> SEQ ID NO 768
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 768

gaccggugag cugaguca                                                   18


<210> SEQ ID NO 769
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 769

ugaccgguga gcugaguc                                                   18


<210> SEQ ID NO 770
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 770

cugaccggug agcugagu                                                   18


<210> SEQ ID NO 771
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 771

acugaccggu gagcugag                                                   18


<210> SEQ ID NO 772
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 772

aacugaccgg ugagcuga                                                   18


<210> SEQ ID NO 773
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 773

gaacugaccg gugagcug                                                   18
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 774

ggaacugacc ggugagcu                                                    18


<210> SEQ ID NO 775
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 775

gggaacugac cggugagc                                                    18


<210> SEQ ID NO 776
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 776

accggugagc ugaguca                                                     17


<210> SEQ ID NO 777
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 777

gaccggugag cugaguc                                                     17


<210> SEQ ID NO 778
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 778

ugaccgguga gcugagu                                                     17


<210> SEQ ID NO 779
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 779

cugaccggug agcugag                                                     17


<210> SEQ ID NO 780
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 780

acugaccggu gagcuga 17

<210> SEQ ID NO 781
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 781

aacugaccgg ugagcug 17

<210> SEQ ID NO 782
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 782

gaacugaccg gugagcu 17

<210> SEQ ID NO 783
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 783

ggaacugacc ggugagc 17

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gaccggugag cugagu 16

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aaccugaggg guuggagaga ggc                                               23


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cuggauguuc agguaaccug agg                                               23


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cgacaucuug acuugcagac gu                                                22


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caucuugacu ugcagacgu                                                    19


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gggugcgaca ucuugacuug caga 24

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ggugcgacau cuugacuugc aga 23

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gugcgacauc uugacuugca ga 22

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ugcgacaucu ugacuugcag a 21

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gcucaccucg cuccccuccg augu 24

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gcucaccucg cuccccuccg aug 23

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cucaccucgc uccccuccga ugu                                            23


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cucaccucgc uccccuccga ug                                             22
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cucaccucgc uccccuccg 19

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 838

ucaccucgcu ccccuccaug uc 22

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ucaccucgcu ccccuccaug u 21

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caccucgcuc cccuccgaug u                                           21


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accucgcucc ccuccauguc cac                                            23


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ccucgcuccc cuccgauguc cacg                                           24
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ccucgcuccc cuccgauguc c                                                21


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ccucgcuccc cuccgauguc                                                  20


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aucauaaauu ucuuaauaac uaca                                             24


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ucauaaauuu cuuaauaacu aca                                              23


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cauaaauuuc uuaauaacua ca                                              22


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auaaauuucu uaauaacuac a                                               21


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<223> OTHER INFORMATION: Synthetic

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uaaauuucuu aauaacuaca                                                 20


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aaauuucuua auaacuaca                                                  19


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aaucauaaau uucuuaauaa cuac                                            24


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aucauaaauu ucuuaauaac uac                                             23


<210> SEQ ID NO 866
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ucauaaauuu cuuaauaacu ac                                              22


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<212> TYPE: RNA
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cauaaauuuc uuaauaacua c                                                 21


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<400> SEQUENCE: 868

auaaauuucu uaauaacuac                                                   20


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uaaauuucuu aauaacuac                                                    19


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gaaucauaaa uuucuuaaua acua                                              24


<210> SEQ ID NO 871
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aaucauaaau uucuuaauaa cua                                               23


<210> SEQ ID NO 872
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aucauaaauu ucuuaauaac ua                                                22


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<223> OTHER INFORMATION: Synthetic

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ucauaaauuu cuuaauaacu a                                                 21
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cauaaauuuc uuaauaacua                                                20


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auaaauuucu uaauaacua                                                 19


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ugaaacauaa auuucuuaau aacu                                           24


<210> SEQ ID NO 877
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acuuucucca ccugucccau ucug 24

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caucuuucga agccacugga ug                                               22


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aucuuucgaa gccacuggau g 21

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cugcuccagg ugacaauucu cc 22

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ugcuccaggu gacaauucuc c 21

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gcuccaggug acaauucuc 19

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cuccagguga caauucuc 18

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accuuaaccu gucgcugcuc c                                               21


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caccuuaacc ugucgcugcu c                                               21


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ucaccuuaac cugucgcugc u                                               21
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auucaccuua accugucgcu g 21

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aauucaccuu aaccugucgc u 21

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caccuuaacc ugucgcugcu 20

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ucaccuuaac cugucgcugc 20

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auucaccuua accugucgcu                                              20


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aauucaccuu aaccugucgc                                              20


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ucaccuuaac cugucgcug                                               19


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uucaccuuaa ccugucgcu                                               19


<210> SEQ ID NO 947
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<212> TYPE: RNA
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auucaccuua accugucgc                                                 19


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aauucaccuu aaccugucg                                                 19


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caccuuaacc ugucgcug                                                  18


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ucaccuuaac cugucgcu                                                  18


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uucaccuuaa ccugucgc                                                  18


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auucaccuua accugucg                                                  18
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uggcuggugg cggcuggugg cgg                                             23


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ggcugguggc ggcugguggc gg                                              22


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gcugguggcg gcugguggcg g                                               21


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cugguggcgg cugguggcgg                                                 20


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ugguggcggc ugguggcgg                                                  19


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cugggucag uggcuggugg cggc                                                24


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<400> SEQUENCE: 961

uggguccagu ggcugguggc ggc                                                23


<210> SEQ ID NO 962
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ggguccagug gcugguggcg gc                                                 22


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gguccagugg cugguggcgg c                                                  21


<210> SEQ ID NO 964
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guccaguggc ugguggcggc                                                    20


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uccaguggcu gguggcggc                                                     19


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ggcugguggc ggcugguggc ggcc                                               24


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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
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gcugguggcg gcugguggcg gcc                                              23


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cugguggcgg cugguggcgg cc                                               22


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ugguggcggc ugguggcggc c                                                21


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gguggcggcu gguggcggcc                                                  20


<210> SEQ ID NO 971
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gcugguggcg gcugguggcg gcca                                             24


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cugguggcgg cugguggcgg cca                                              23
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cugguggcgg cugguggcgg ccag                                            24


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guggcggcug guggcggcca gg                                              22


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guggcggcug guggcggcca ggc                                              23


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cggcuggugg cggccaggc                                                    19


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acccuggguc caguggcugg uggc                                              24


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cccugggucc aguggcuggu ggc                                               23


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cuggguccag uggcuggugg c                                                 21


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uggguccagu ggcugguggc                                                    20


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gacccugggu ccaguggcug gugg                                               24


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<212> TYPE: RNA
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<220> FEATURE:
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acccuggguc caguggcugg ugg                                                23


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cccuggucc aguggcuggu gg                                                  22


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<400> SEQUENCE: 1004

ccuggrucca guggcuggug g                                                  21


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cuggguccag uggcuggugg                                                    20


<210> SEQ ID NO 1006
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<212> TYPE: RNA
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agacccuggg uccaguggcu ggug                                               24


<210> SEQ ID NO 1007
<211> LENGTH: 23
<212> TYPE: RNA
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<400> SEQUENCE: 1007

gacccugggu ccaguggcug gug                                              23


<210> SEQ ID NO 1008
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<212> TYPE: RNA
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<400> SEQUENCE: 1008

acccuggguc caguggcugg ug                                               22


<210> SEQ ID NO 1009
<211> LENGTH: 21
<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 1009

cccuggucc aguggcuggu g                                                 21


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<212> TYPE: RNA
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<400> SEQUENCE: 1010

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<210> SEQ ID NO 1011
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<212> TYPE: RNA
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<220> FEATURE:
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cgggcaauug uggagacccu gggu                                             24


<210> SEQ ID NO 1012
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 1012

gggcaauugu ggagacccug ggu                                              23


<210> SEQ ID NO 1013
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ggcaauugug gagacccugg gu                                               22
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<210> SEQ ID NO 1015
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caauugugga gacccugggu                                                20


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cgggcaauug uggagacccu ggg                                            23


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gggcaauugu ggagacccug gg                                             22


<210> SEQ ID NO 1019
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ggcaauugug gagacccugg g                                              21


<210> SEQ ID NO 1020
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<400> SEQUENCE: 1020

gcaauugugg agacccuggg 20

<210> SEQ ID NO 1021
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 1021

gugcucgggc aauuguggag accc 24

<210> SEQ ID NO 1022
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ugcucgggca auuguggaga ccc 23

<210> SEQ ID NO 1023
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<400> SEQUENCE: 1023

gcucgggcaa uuguggagac cc 22

<210> SEQ ID NO 1024
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1024

cucgggcaau uguggagacc c 21

<210> SEQ ID NO 1025
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1025

ucgggcaauu guggagaccc 20

<210> SEQ ID NO 1026
<211> LENGTH: 24
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1026

caagugcucg ggcaauugug gaga 24

<210> SEQ ID NO 1027
<211> LENGTH: 23
<212> TYPE: RNA

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<220> FEATURE:
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<400> SEQUENCE: 1027

aagugcucgg gcaauugugg aga                                              23


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agugcucggg caauugugga ga                                               22


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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1029

gugcucgggc aauuguggag a                                                21


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<400> SEQUENCE: 1030

ugcucgggca auuguggaga                                                  20


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ccaagugcuc gggcaauugu ggag                                             24


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caagugcucg ggcaauugug gag                                              23


<210> SEQ ID NO 1033
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<212> TYPE: RNA
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<400> SEQUENCE: 1033

aagugcucgg gcaauugugg ag                                               22
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agugcucggg caauugugga g                                              21


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gugcucgggc aauuguggag                                                20


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<400> SEQUENCE: 1036

ugauuccaag ugcucgggca auug                                           24


<210> SEQ ID NO 1037
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<400> SEQUENCE: 1037

gauuccaagu gcucgggcaa uug                                            23


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<400> SEQUENCE: 1038

auuccaagug cucgggcaau ug                                             22


<210> SEQ ID NO 1039
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<400> SEQUENCE: 1039

uuccaagugc ucgggcaauu g                                              21


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uccaagugcu cgggcaauug                                                   20


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ccaagugcuc gggcaauug                                                    19


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cugauuccaa gugcucgggc aauu                                              24


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cugauuccaa gugcucgggc aau                                               23


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<400> SEQUENCE: 1044

cugauuccaa gugcucgggc aa                                                22


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<223> OTHER INFORMATION: Synthetic

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cugauuccaa gugcucgggc a                                                 21


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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1046

cugauuccaa gugcucgggc                                                   20


<210> SEQ ID NO 1047
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1047

cugauuccaa gugcucggg 19

<210> SEQ ID NO 1048
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1048

acugauucca agugcucggg caau 24

<210> SEQ ID NO 1049
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1049

acugauucca agugcucggg caa 23

<210> SEQ ID NO 1050
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1050

acugauucca agugcucggg ca 22

<210> SEQ ID NO 1051
<211> LENGTH: 21
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acugauucca agugcucggg c 21

<210> SEQ ID NO 1052
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<212> TYPE: RNA
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<400> SEQUENCE: 1052

acugauucca agugcucggg 20

<210> SEQ ID NO 1053
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<400> SEQUENCE: 1053

acugauucca agugcucgg 19

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<400> SEQUENCE: 1054

uacugauucc aagugcucgg gcaa                                              24


<210> SEQ ID NO 1055
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<220> FEATURE:
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<400> SEQUENCE: 1055

uacugauucc aagugcucgg gca                                               23


<210> SEQ ID NO 1056
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<212> TYPE: RNA
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<400> SEQUENCE: 1056

uacugauucc aagugcucgg gc                                                22


<210> SEQ ID NO 1057
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<212> TYPE: RNA
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<400> SEQUENCE: 1057

uacugauucc aagugcucgg g                                                 21


<210> SEQ ID NO 1058
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<212> TYPE: RNA
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<400> SEQUENCE: 1058

uacugauucc aagugcucgg                                                   20


<210> SEQ ID NO 1059
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<212> TYPE: RNA
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<400> SEQUENCE: 1059

uacugauucc aagugcucg                                                    19


<210> SEQ ID NO 1060
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic
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uuacugauuc caagugcucg ggca                                        24


<210> SEQ ID NO 1061
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 1061

uuacugauuc caagugcucg ggc                                         23


<210> SEQ ID NO 1062
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<220> FEATURE:
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<400> SEQUENCE: 1062

uuacugauuc caagugcucg gg                                          22


<210> SEQ ID NO 1063
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1063

uuacugauuc caagugcucg g                                           21


<210> SEQ ID NO 1064
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1064

uuacugauuc caagugcucg                                             20


<210> SEQ ID NO 1065
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1065

uuacugauuc caagugcuc                                              19


<210> SEQ ID NO 1066
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1066

cuuacugauu ccaagugcuc gggc                                        24


<210> SEQ ID NO 1067
<211> LENGTH: 23
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1067

cuuacugauu ccaagugcuc ggg                                               23


<210> SEQ ID NO 1068
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1068

cuuacugauu ccaagugcuc gg                                                22


<210> SEQ ID NO 1069
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1069

cuuacugauu ccaagugcuc g                                                 21


<210> SEQ ID NO 1070
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1070

cuuacugauu ccaagugcuc                                                   20


<210> SEQ ID NO 1071
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1071

cuuacugauu ccaagugcu                                                    19


<210> SEQ ID NO 1072
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1072

ccuuacugau uccaagugcu cggg                                              24


<210> SEQ ID NO 1073
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1073

ccuuacugau uccaagugcu cgg                                               23
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<210> SEQ ID NO 1074
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1074

ccuuacugau uccaagugcu cg                                              22


<210> SEQ ID NO 1075
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1075

ccuuacugau uccaagugcu c                                               21


<210> SEQ ID NO 1076
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1076

ccuuacugau uccaagugcu                                                 20


<210> SEQ ID NO 1077
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1077

ccuuacugau uccaagugc                                                  19


<210> SEQ ID NO 1078
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1078

accuuacuga uuccaagugc ucgg                                            24


<210> SEQ ID NO 1079
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1079

accuuacuga uuccaagugc ucg                                             23


<210> SEQ ID NO 1080
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 1080

accuuacuga uuccaagugc uc 22

<210> SEQ ID NO 1081
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1081

accuuacuga uuccaagugc u 21

<210> SEQ ID NO 1082
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1082

accuuacuga uuccaagugc 20

<210> SEQ ID NO 1083
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1083

accuuacuga uuccaagug 19

<210> SEQ ID NO 1084
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1084

aaccuuacug auuccaagug cucg 24

<210> SEQ ID NO 1085
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1085

aaccuuacug auuccaagug cuc 23

<210> SEQ ID NO 1086
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1086

aaccuuacug auuccaagug cu 22

<210> SEQ ID NO 1087
<211> LENGTH: 21
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1087

aaccuuacug auuccaagug c                                              21


<210> SEQ ID NO 1088
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1088

aaccuuacug auuccaagug                                                20


<210> SEQ ID NO 1089
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1089

aaccuuacug auuccaagu                                                 19


<210> SEQ ID NO 1090
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR1-flop exon

<400> SEQUENCE: 1090

aaatccagta aacctggcag tgttaaaact gaacgagcag ggcttttgga caaattgaaa     60

aacaaatggt ggtacgacag agggcgagtg cggcagcggg ggaggtgact ccaag         115


<210> SEQ ID NO 1091
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR2-flop exon

<400> SEQUENCE: 1091

aaatgcggtt aacctcgcag tactaaaact gaatgaacaa ggcctgttgg acaaattgaa     60

aaacaaatgg tggtacgaca aaggagagtg cggcagcggg ggaggtgatt ccaag         115


<210> SEQ ID NO 1092
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR3-flop exon

<400> SEQUENCE: 1092

aaatgctgtt aacctggcag tattaaaact gaatgagcaa ggcctcttgg acaaattgaa     60

aaacaaatgg tggtacgaca aaggagagtg cggcagcggg ggcggtgact ccaag         115


<210> SEQ ID NO 1093
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: mGluR4-flop exon

<400> SEQUENCE: 1093

aaatgctgtt aacctcgcag ttttaaaact gaatgaacaa ggcctcttgg acaaattgaa 60

aaacaaatgg tggtacgaca aaggagaatg tggcagcggg ggaggtgact ccaag 115

<210> SEQ ID NO 1094
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR1-flip exon

<400> SEQUENCE: 1094

aggtcccgta aacctagcgg ttttgaaact cagtgagcaa ggcgtcttag acaagctgaa 60

aagcaaatgg tggtacgata aaggggaatg tggaagcaag gactccggaa gtaag 115

<210> SEQ ID NO 1095
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR2-flip exon

<400> SEQUENCE: 1095

aaccccagta aatcttgcag tattgaaact cagtgagcaa ggcgtcttag acaagctgaa 60

aaacaaatgg tggtacgata aaggtgaatg tggagccaag gactcgggaa gtaag 115

<210> SEQ ID NO 1096
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR3-flip exon

<400> SEQUENCE: 1096

aacgcctgta aaccttgcag tattgaaact cagtgaacaa ggcatcttag acaagctgaa 60

aaacaaatgg tggtacgata agggggaatg tggagccaag gactccggga gtaag 115

<210> SEQ ID NO 1097
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR4-flip exon

<400> SEQUENCE: 1097

aactcctgta aaccttgccg ttttgaaact cagtgaggca ggcgtcttag acaagctgaa 60

aaacaaatgg tggtacgata aaggtgaatg tggacccaag gactcgggaa gcaag 115

<210> SEQ ID NO 1098
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR4-flip with exon skipped

<400> SEQUENCE: 1098

gaagaactcc tgtaaacctt gccgttttga aagataaagg tgaatgtgga cccaaggact 60

cgggaagcaa ggtcagtcgg tgc 83

<210> SEQ ID NO 1099

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<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR1-flip with exon skipped

<400> SEQUENCE: 1099

gaagaggtcc cgtaaaccta gcggttttga aagataaagg ggaatgtgga agcaaggact     60

ccggaagtaa ggtcagtcac ctg                                             83


<210> SEQ ID NO 1100
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR2-flip with exon skipped

<400> SEQUENCE: 1100

gaagaacccc agtaaatctt gcagtattga aagataaagg tgaatgtgga gccaaggact     60

cgggaagtaa ggtcagttgc tgc                                             83


<210> SEQ ID NO 1101
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mGluR3-flip with exon skipped

<400> SEQUENCE: 1101

gaagaacgcc tgtaaacctt gcagtattga aagataaggg ggaatgtgga gccaaggact     60

ccgggagtaa ggtcagtcgc tga                                             83


<210> SEQ ID NO 1102
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense oligonucleotide

<400> SEQUENCE: 1102

auucccccuu acaccucggu ucc                                             23


<210> SEQ ID NO 1103
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense oligonucleotide

<400> SEQUENCE: 1103

aggcccucau uccagucagc ga                                              22


<210> SEQ ID NO 1104
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense oligonucleotide

<400> SEQUENCE: 1104

acauuuggaa cgucauaacu                                                 20


<210> SEQ ID NO 1105
<211> LENGTH: 23
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense oligonucleotide

<400> SEQUENCE: 1105

cccccuuaca ccucgguucc uga                                               23


<210> SEQ ID NO 1106
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: GluR2 skip exon 15 sequence

<400> SEQUENCE: 1106

tgaagaaccc cagtaaatct tgcagtattg tgtggagcca aggactcggg aagtaaggtc      60

agttgctgca                                                              70


<210> SEQ ID NO 1107
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1107

acuucuuggg gucauuuaga acguc                                             25


<210> SEQ ID NO 1108
<211> LENGTH: 16
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1108

acaccucggu uccuga                                                       16


<210> SEQ ID NO 1109
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1109

ccuucauucc agucaacgac gu                                                22


<210> SEQ ID NO 1110
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1110

ccuucauucc agucaacgac g                                                 21


<210> SEQ ID NO 1111
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1111
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gggggucauuu agaacgucau aac                                        23


<210> SEQ ID NO 1112
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1112

ggggucauuu agaacgucau                                             20


<210> SEQ ID NO 1113
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1113

ccuucauucc agucaacga                                              19
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What is claimed:

1. A composition comprising a splice modulating oligonucleotide (SMO) that specifically binds a complementary sequence of a pre-mRNA that undergoes splicing to form a mRNA encoding a glutamate activated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit (GluR), wherein said SMO is selected from any of SEQ ID NOs: 86, 123, 143, 228, 243, 269, 306, 318, 442, or 496, or a sequence having at least 90% identity over the full sequence of any of SEQ ID NOs: 86, 123, 143, 228, 243, 269, 306, 318, 442, or 496.

2. The composition according to claim **1**, wherein at least one nucleotide in said SMO contains a non-naturally occurring modification comprising at least one of a chemical composition of phosphorothioate 2'-O-methyl, phosphorothioate 2'-MOE, locked nucleic acid (LNA), peptide nucleic acid (PNA), phosphorodiamidate morpholino, or any combination thereof.

3. The composition according to claim **1**, further comprising a pharmaceutically acceptable carrier.

4. A composition according to claim **1**, wherein said SMO is a sequence having at least 95% identity over the full sequence of any of SEQ ID NOs: 86, 123, 143, 228, 243, 269, 306, 318, 442, or 496.

5. A composition according to claim **4**, wherein said SMO is selected from any of SEQ ID NOs: 86, 123, 143, 228, 243, 269, 306, 318, 442, or 496.

6. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 123.

7. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 243.

8. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 269.

9. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 306.

10. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 318.

11. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 442.

12. The composition according to claim **1**, wherein said SMO is a sequence having at least 90% identity over the full sequence of SEQ ID NO: 496.

13. A composition comprising a splice modulating oligonucleotide (SMO) that specifically binds a complementary sequence of a pre-mRNA that undergoes splicing to form a mRNA encoding a glutamate activated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit (GluR), wherein said SMO is SEQ ID NO: 228, or a sequence having at least 90% identity over the full sequence of SEQ ID NO: 228.

14. The composition according to claim **13**, wherein said SMO is a sequence having at least 95% identity over the full sequence of SEQ ID NO: 228.

15. The composition according to claim **14**, wherein said SMO is SEQ ID NO: 228.

16. A composition comprising a splice modulating oligonucleotide (SMO) that specifically binds a complementary sequence of a pre-mRNA that undergoes splicing to form a mRNA encoding a glutamate activated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit (GluR), wherein said SMO is SEQ ID NO: 86 or 143, or a sequence having at least 90% identity over the full sequence of SEQ ID NO: 86 or 143.

17. The composition according to claim **16**, wherein said SMO is a sequence having at least 95% identity over the full sequence of SEQ ID NO: 86.

18. The composition according to claim **17**, wherein said SMO is SEQ ID NO: 86.

19. The composition according to claim **16**, wherein said SMO is a sequence having at least 95% identity over the full sequence of SEQ ID NO: 143.

20. The composition according to claim **19**, wherein said SMO is SEQ ID NO: 143.

* * * * *